(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/02622 A2

(51) International Patent Classification[7]: C07K 14/47

(21) International Application Number: PCT/US01/20872

(22) International Filing Date: 29 June 2001 (29.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/608,352 29 June 2000 (29.06.2000) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/608,352 (CIP)
Filed on 29 June 2000 (29.06.2000)

(71) Applicant *(for all designated States except US)*: THE SALK INSTITUTE FOR BIOLOGICAL STUDIES [US/US]; 10010 North Torrey Pines Road, San Diego, CA 92037 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: NOEL, Joseph, P. [US/US]; 7280 Park Village Road, San Diego, CA 92129 (US). VERDACIA, Mark [US/US]; 415 Gravilla Street, #11, La Jolla, CA 92037 (US). HUNTER, Tony [GB/US]; 4578 Vista De La Patria, Del Mar, CA 92015 (US). HUANG, Han-Kuei [—/US]; 5438 Lauretta Street, Apt. A, San Diego, CA 92110 (US).

(74) Agents: REITER, Stephen, E. et al.; Foley & Lardner, P.O. Box 80278, San Diego, CA 92138-0278 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/02622 A2

(54) Title: CRYSTAL STRUCTURE OF SURVIVIN

(57) Abstract: Provided is the structure of an inhibitor of apoptosis protein (IAP). Å 2.58 A crystal structure of a human survivin point mutant (L54M) determined by Multiple Wavelength Anomalous Dispersion (MAD) using the endogenously bound Zn^{+2} ions is provided. Methods of using the crystal structure and atomic coordinates fo the development of IAP binding agents is also provided. In addition, the disclosure provides computer programs on computer readable medium for use in developing iAP binding agents.

CRYSTAL STRUCTURE OF SURVIVIN

RELATED APPLICATIONS

This application claims the benefit of U.S. Application No. 09/608,352, filed June 29, 2000, now pending, which is hereby incorporated by reference herein in its entirety.

ACKNOWLEDGMENT

This invention was made with United States Government support under Grants No. GM-57533 and CA-80100, awarded by the National Institutes of Health. The Government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates to crystals of the inhibitors of apoptosis protein (IAP) family and more particularly to the high resolution structure of survivin obtained by X-ray diffraction. In addition, the invention relates to methods of using the structure coordinates of the survivin IAP and mutants thereof to screen and design compounds that bind to or interact with IAP proteins and IAP protein family members.

BACKGROUND

Advances in molecular biology have allowed the development of biological agents useful in modulating protein or nucleic acid activity or expression, respectively. Many of these advances are based on identifying the primary sequence of the molecule to be modulated. For example, determining the nucleic acid sequence of DNA or RNA allows the development of antisense or ribozyme molecules. Similarly, identifying the primary sequence allows for the identification of sequences that may be useful in creating monoclonal antibodies. However, often the primary sequence of a protein is insufficient to develop therapeutic or diagnostic molecules due to the secondary, tertiary or quartenary structure of the protein from which the primary sequence is obtained. The process of designing potent and specific inhibitors or activators has improved with the arrival of techniques for

MISSING AT THE TIME OF PUBLICATION

determining the three-dimensional structure of an enzyme or polypeptide to be modulated.

Cells die as a result of many factors and processes. One process is apoptosis. The apoptosis process, or programmed cell death, often occurs so rapidly that in some biological systems the apoptotic process is difficult to ascertain. Indeed, it has been only in the past few years that the involvement of apoptosis in a wide spectrum of biological processes has become recognized. Apoptosis is a fundamental physiological pathway of cell death, highly conserved throughout evolution, and plays a major role in development, viral pathogenesis, cancer, autoimmune diseases and neurodegenerative disorders.

Inappropriate changes in apoptosis may cause or contribute to a variety of diseases, including AIDS, neurodegenerative diseases (*e.g.* Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS)), retinitis pigmentosa and other diseases of the retina, myelodysplastic syndrome (*e.g.*, aplastic anemia), toxin-induced liver disease (*e.g.*, alcoholism), ischemic injury (*e.g.*, myocardial infarction, stroke, and reperfusion injury), and the like. In addition, disruption of normally occurring apoptosis has been implicated in the development of some cancers (*e.g.*, follicular lymphoma, p53 carcinomas, and hormone dependent tumors), autoimmune disorders (*e.g.*, lupus erythematosis and multiple sclerosis), viral infections (*e.g.*, herpes virus, poxvirus, and adenovirus infections), and the like.

Survivin (16.5 kDa) is an inhibitor of apoptosis protein (IAP) family member that temporally and spatially localizes to microtubule organizing centers (MTOC) during mitosis (Li, F. *et al.* Nature 396:580-583, 1998). Localization of survivin to this spindle apparatus is functionally linked to its ability to circumvent both Bax and Fas induced programmed cell death (Tamm, I. *et al.* Cancer Res. 58:5315-5320, 1998). IAPs are characterized by the presence of one or more baculovirus IAP repeat (BIR) domains. These 70-residue zinc-binding modules often function as potent inhibitors of cell death proteases (Liston, P. *et al.* Nature 379:349-353, 1996; Uren, A. G. *et al.* Proc. Natl. Acad. Sci USA 93:4974-4978, 1996). In many cases, IAPs also contain a caspase recruiting domain (CARD), and a RING finger domain (Deveraux and Reed, Genes Dev. 13:239-252, 1999). Human survivin, 142 residues in length, contains a

single BIR domain located in its N-terminal half and a C-terminal region predicted to form a coiled-coil. Survivin is unique among IAPs in that it is undetectable in normal differentiated tissue but highly expressed in the developing embryo and in rapidly dividing cells (Ambrosini *et al.*, Nature Med. 3:917-921, 1997).

The design of new, highly specific agents capable of modulating apoptosis represents an important need in the pharmaceutical industry. Such agents can serve as effective chemotherapeutic agents for the treatment of a variety of disorders characterized by inappropriate cell proliferation, including cancer and infectious diseases. The invention disclosed herein addresses this and related needs, as will become apparent upon review of the specification and appended claims.

SUMMARY OF THE INVENTION

In an effort to elucidate IAPs' critical role in proliferating cells, a 2.58 Å crystal structure of a human survivin point mutant (L54M) determined by Multiple Wavelength Anomalous Dispersion (MAD) using the endogenously bound Zn^{+2} ions is provided. Methods of using the crystal structure and atomic coordinates for the development of IAP binding agents are also provided. In addition, the disclosure provides computer programs on computer readable medium for use in developing IAP binding agents useful in modulating apoptosis and treating cell proliferative disorders.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 collectively shows the overall architecture of human survivin. Figure 1a shows a ribbon representation of the survivin dimer. The Zn^{+2} ion is shown as a sphere. Coordination bonds are shown as dotted spheres. Two monomers are depicted. Figure 1b is an orthogonal view of the ribbon representation shown in Figure 1a. Figure 1c, shows a GRASP representation of the survivin solvent accessible surface shaded to reflect the underlying electrostatic surface, where shaded areas are positive or negative, and white is neutral. The orientation is the same as in Figure 1a. Figure 1d is an orthogonal view of that shown in Figure 1c. Figure 1e is a close-up view of the dimer interface comprising the intermolecular β-sheet. Alpha carbons are numbered and side chains are omitted

for clarity. Boxed numbers correspond to alpha carbons in one survivin monomer. Hydrogen bonds are shown as dotted spheres. The orientation is identical to that shown in Figures 1a and 1c. Figure 1f is a close-up view of the dimer interface comprising the hydrophobic contacts. Side chains numbered and boxed correspond to the same monomer as in Figure 1e. The orientation is identical to that shown in Figures 1b and 1d.

Figure 2 shows the sequence alignment of six representative BIR domain containing proteins. Secondary structural elements for survivin are shown and the analogous features for XIAP BIR2 are depicted in gray shaded text. Residues in dark gray boxes correspond to hydrophobic amino acids at the dimer interface, inverted white on black text corresponds to residues in the basic patch; hatched boxes correspond to amino acids comprising the zinc coordination sphere; boxes with asterisks correspond to residues in the acidic patch; the dark gray boxes in the 5th and 6th rows from the bottom are putative phosphorylation sites; light gray boxes delineate positions along α6 forming a hydrophobic patch; and gray-boxed text depict positions previously shown to participate in caspase inhibition. h refers to human survivin (SEQ ID NO: 3), m refers to mouse survivin (SEQ ID NO: 5), c refers to *C. elegans* survivin.

Figure 3 collectively is an enlarged view of survivin's sub-domains. Figure 3a, is a perspective and close-up view of the Zn^{+2} binding site on one survivin monomer. The depicted orientation corresponds to that pictured in Figure 1a. Figure 3b is a perspective and close-up view of the sulphate binding site. The depicted orientation corresponds to that pictured in Figure 1b. Figure 3c shows an expanded view of one survivin monomer illustrating the location of the α6 hydrophobic surface. The orientation corresponds to that shown in Figure 1b.

Figure 4 shows an example of a computer system in block diagram form.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, a method of predicting a binding agent for an inhibitor of apoptosis protein (IAP) is provided. The method comprises modeling a potential binding agent that interacts with one or more functional domains of a survivin polypeptide (*i.e.*, an IAP), defined by a plurality of atomic coordinates of the survivin polypeptide, and determining the ability of the potential binding agent to modulate a survivin biological function (e.g., apoptosis), thereby predicting an IAP binding agent.

In another aspect, the invention provides a computer program on a computer readable medium, the computer program having instructions to cause a computer to model a potential binding agent that can bind an IAP molecule defined by a plurality of atomic coordinates.

An IAP polypeptide typically has at least one BIR domain and a ring zinc finger domain which is capable of modulating (inhibiting or enhancing) apoptosis in a cell or tissue. An IAP gene or polypeptide also includes any member of the family of apoptosis inhibitory genes characterized by their ability to modulate apoptosis and having at least 20%, preferably 30%, and more preferably 50% amino acid sequence identity to at least one of the conserved regions of one of the IAP members described herein (*e.g.*, either the BIR or ring zinc finger domains from xiap, hiap1 and hiap2, m-xiap, a C-terminal helix structure of survivin, and the like). Representative members of the IAP gene family include, for example, the xiap, hiap1, and hiap2 genes of humans, the m-xiap gene of the mouse, and the like. By "IAP protein" is meant a polypeptide encoded by an IAP gene.

A "BIR domain" typically has in the range of 65 up to 68 amino acid residues and has an amino acid consensus sequence of: Xaa1 Xaa1 Xaa1 Arg Leu Xaa1 Thr Phe Xaa1 Xaa1 Trp Pro Xaa2 Xaa1 Xaa1 Xaa2 Xaa2 Xaa1 Xaa1 Xaa1 Xaa1 Leu Ala Xaa1 Ala Gly Phe Tyr Tyr Xaa1 Gly Xaa1 Xaa1 Asp Xaa1 Val Xaa1 Cys Phe Xaa1 Cys Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 Trp Xaa1 Xaa1 Xaa1 Asp Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 His Xaa1 Xaa1 Xaa1 Xaa1 Pro Xaa1 Cys Xaa1 Phe Val, wherein Xaa1 is any amino acid and Xaa2 is any amino acid or is absent (SEQ ID NO:1).

A "ring zinc finger" or "RZF" typically has in the range of 45 to 46 amino acid residues and has a consensus sequence of: Glu Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 Xaa2 Xaa1 Xaa1 Xaa1 Cys Lys Xaa3 Cys Met Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 Xaa3 Xaa1 Phe Xaa1 Pro Cys Gly His Xaa1 Xaa1 Xaa1 Cys Xaa1 Xaa1 Cys Ala Xaa1 Xaa1 Xaa1 Xaa1 Xaa1 Cys Pro Xaa1 Cys, wherein Xaa1 is any amino acid, Xaa2 is Glu or Asp, and Xaa3 is Val or Ile (SEQ ID NO: 2).

By "modulating apoptosis" is meant increasing or decreasing the number of cells which undergo apoptosis in a given cell population. Typically the cell population is selected from T-cells, neuronal cells, fibroblasts, or any other cell line known to undergo apoptosis in a laboratory setting (*e.g.*, the baculovirus infected insect cells). It will be appreciated that the degree of modulation provided by an IAP or modulating agent (*e.g.*, a binding agent, inhibitor, or activator) will vary and will depend upon the assay conditions. An inhibitor of apoptosis includes any agent that decreases the number of cells which undergo apoptosis relative to an untreated control.

A polypeptide is a chain of amino acids, regardless of length or post-translational modification (*e.g.*, glycosylation or phosphorylation). A polypeptide or protein refers to a polymer in which the monomers are amino acid residues which are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used, the L-isomers being typical. An IAP or survivin polypeptide is intended to encompass an amino acid sequence as set forth in SEQ ID NOs: 3 or 4, mutants, variants and conservative substitutions thereof comprising L- or D- amino acids and include modified forms thereof, such as glycoproteins. Accordingly, the polypeptides of the invention are intended to cover naturally occurring proteins, as well as those which are recombinantly or synthetically synthesized. Polypeptide or protein fragments are also encompassed by the invention. Fragments can have the same or substantially the same amino acid sequence as the naturally occurring protein. A polypeptide or peptide having substantially the same sequence means that an amino acid sequence is largely, but not entirely, the same, but retains a functional activity of the sequence to which it is related. In general polypeptides of the invention include peptides, or full length

protein, that contain substitutions, deletions, or insertions into the protein backbone, that would still have an approximately 70%-90% homology to the original protein over the corresponding portion. A yet greater degree of departure from homology is allowed if like-amino acids, *i.e.* conservative amino acid substitutions, do not count as a change in the sequence.

A polypeptide which is substantially related to a naturally occuring protein but for a conservative variation is also contemplated to be within the scope of the present invention. A conservative variation denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine, for another hydrophobic residue, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. Other illustrative examples of conservative substitutions include the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine, glutamine, or glutamate; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; valine to isoleucine to leucine. The term "conservative variation" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.

The term "positively charged amino acid" includes any naturally occurring or unnatural amino acid having a positively charged side chain under normal physiological conditions. Examples of positively charged naturally occurring amino acids are arginine, lysine and histidine.

The term "negatively charged amino acid" includes any naturally occurring or unnatural amino acid having a negatively charged side chain under normal physiological conditions. Examples of negatively charged naturally occurring amino acids are aspartic acid and glutamic acid.

The term "hydrophobic amino acid" means any amino acid having an uncharged, nonpolar side chain that is relatively insoluble in water. Examples of naturally occurring hydrophobic amino acids are alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine.

The term "hydrophilic amino acid" means any amino acid having an uncharged, polar side chain that is relatively soluble in water. Examples of naturally occurring hydrophilic amino acids are serine, threonine, tyrosine, asparagine, glutamine, and cysteine.

Modifications and substitutions are not limited to replacement of amino acids. For a variety of purposes, such as increased stability, solubility, or configuration concerns, one skilled in the art will recognize the potential value of introducing, (by deletion, replacement, or addition) other modifications. Examples of such other modifications include incorporation of rare amino acids, D-amino acids, glycosylation sites, cytosine for specific disulfide bridge formation, and the like. The modified peptides can be chemically synthesized, or the isolated gene can be site-directed mutagenized, or a synthetic gene can be synthesized and expressed in bacteria, yeast, baculovirus, tissue culture, and the like. An example of a modification providing increased solubility includes the L54M mutation (SEQ ID NO: 4) described below. The mutation increases the hydrophilic nature of the survivin polypeptide compared to the wild type polypeptide. Accordingly, other modifications which alter the hydrophilic nature or hydrophobic nature of the survivin polypeptide are encompassed by the present invention.

IAP or survivin polypeptides of the invention include survivin polypeptides from invertebrates, mammals and humans and include sequences as set forth in SEQ ID NOs: 3, 4, and 5, as well as sequences that have at least 70% homology to the sequences of SEQ ID NOs: 3, 4, and 5, fragments, variants, or conservative substitutions of any of the foregoing sequences. Other survivin related polypeptide sequences are applicable to the methods of the present invention (see, for example, Conway *et al.* Blood, 95(4):1435-1442 (2000), which is incorporated by reference herein).

The term "variant" refers to polypeptides which are modified at one or more amino acid residues yet still retain the biological activity of an IAP or survivin polypeptide. Variants can be produced by any number of means known in the art, including, for example, such methods as error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis; and the like, as well as any combination of two or more thereof.

By "substantially identical" is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% homology to a reference amino acid or nucleic acid sequence.

Homology or identity is often measured using sequence analysis software (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). Such software matches similar sequences by assigning degrees of homology to various deletions, substitutions and other modifications. The terms "homology" and "identity" in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same when compared and aligned for maximum correspondence over a comparison window or designated region as measured using any number of sequence comparison algorithms or by manual alignment and visual inspection.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions falling in the range of about 20 to about 600, usually from about 50 to about 200, more usually from about 100 to about 150 in which

a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482, 1981, by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol 48:443, 1970, by the search for similarity method of person & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), by manual alignment and visual inspection, and the like. Other algorithms for determining homology or identity include, for example, in addition to a BLAST program (Basic Local Alignment Search Tool at the National Center for Biological Information), ALIGN, AMAS (Analysis of Multiply Aligned Sequences), AMPS (Protein Multiple Sequence Alignment), ASSET (Aligned Segment Statistical Evaluation Tool), BANDS, BESTSCOR, BIOSCAN (Biological Sequence Comparative Analysis Node), BLIMPS (BLocks IMProved Searcher), FASTA, Intervals & Points, BMB, CLUSTAL V, CLUSTAL W, CONSENSUS, LCONSENSUS, WCONSENSUS, Smith-Waterman algorithm, DARWIN, Las Vegas algorithm, FNAT (Forced Nucleotide Alignment Tool), Framealign, Framesearch, DYNAMIC, FILTER, FSAP (Fristensky Sequence Analysis Package), GAP (Global Alignment Program), GENAL, GIBBS, GenQuest, ISSC (Sensitive Sequence Comparison), LALIGN (Local Sequence Alignment), LCP (Local Content Program), MACAW (Multiple Alignment Construction & Analysis Workbench), MAP (Multiple Alignment Program), MBLKP, MBLKN, PIMA (Pattern-Induced Multi-sequence Alignment), SAGA (Sequence Alignment by Genetic Algorithm) and WHAT-IF. Such alignment programs can also be used to screen genome databases to identify polynucleotide sequences having substantially identical sequences. A number of genome databases are available, for example, a substantial portion of the human genome is available as part of the Human Genome Sequencing Project (J. Roach, http://weber.u.Washington.edu/~roach/human_genome_progress 2.html) (Gibbs, 1995). At least twenty-one other genomes have already been sequenced, including, for example, *M. genitalium* (Fraser *et al.*, 1995), M. jannaschii (Bult *et al.*, 1996), *H. influenzae* (Fleischmann *et al.*, 1995), *E. coli* (Blattner *et al.*, 1997), and yeast (*S. cerevisiae*) (Mewes *et al.*, 1997), and *D. melanogaster* (Adams *et al.*,

2000). Significant progress has also been made in sequencing the genomes of model organisms, such as mouse, *C. elegans*, and *Arabadopsis sp*. Several databases containing genomic information annotated with some functional information are maintained by different organizations, and are accessible via the internet, for example, http://wwwtigr.org/tdb; http://www.genetics.wisc.edu; http://genome-www.stanford.edu/~ball; http://hiv-web.lanl.gov; http://www.ncbi.nlm.nih.gov; http://www.ebi.ac.uk; http://Pasteur.fr/other/biology; and http://www.genome.wi.mit.edu.

Examples of useful algorithms are BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25:3389-3402, 1977, and Altschul *et al.*, J. Mol. Biol. 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih. gov). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al., supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectations (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff &

Henikoff, Proc. Natl. Acad. Sci. USA 89:10915, 1989) alignments (B) of 50, expectation (E) of 10, M=5, N= -4, and a comparison of both strands.

The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin & Altschul, Proc. Natl. Acad. Sci. USA 90:5873, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

In one embodiment, protein and nucleic acid sequence homologies are evaluated using the Basic Local Alignment Search Tool ("BLAST"). In particular, five specific BLAST programs are used to perform the following task:

(1) BLASTP and BLAST3 compare an amino acid query sequence against a protein sequence database;

(2) BLASTN compares a nucleotide query sequence against a nucleotide sequence database;

(3) BLASTX compares the six-frame conceptual translation products of a query nucleotide sequence (both strands) against a protein sequence database;

(4) TBLASTN compares a query protein sequence against a nucleotide sequence database translated in all six reading frames (both strands); and

(5) TBLASTX compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (*i.e.*, aligned) by means of a scoring matrix, many of which are known in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet *et al.*, Science 256:1443-1445, 1992; Henikoff and Henikoff, Proteins 17:49-61, 1993). Less preferably, the PAM or PAM250 matrices may also be used (see, *e.g.*, Schwartz and Dayhoff, eds., 1978, *Matrices for Detecting Distance Relationships: Atlas of Protein Sequence and Structure*, Washington: National Biomedical Research Foundation). BLAST programs are accessible through the U.S. National Library of Medicine, *e.g.*, at www.ncbi.nlm.nih.gov.

The parameters used with the above algorithms may be adapted depending on the sequence length and degree of homology studied. In some embodiments, the parameters may be the default parameters used by the algorithms in the absence of instructions from the user.

By a "substantially pure polypeptide" is meant an IAP polypeptide which has been separated from components which naturally accompany it. Typically, the polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, IAP polypeptide. A substantially pure IAP polypeptide may be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid encoding an IAP polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method (*e.g.*, column chromatography, polyacrylamide gel electrophoresis, by HPLC analysis, and the like).

One aspect of the invention resides in obtaining crystals of the IAP polypeptide survivin of sufficient quality to determine the three dimensional (tertiary) structure of the protein by X-ray diffraction methods. The knowledge obtained concerning the three-dimensional structure of survivin can be used in the

determination of the three dimensional structure of other IAP proteins. The binding agent can also be predicted by various computer models. Based on the structural coordinates of the survivin polypeptide (*i.e.*, the three dimensional protein structure), as described herein, small molecules which mimic or are capable of interacting with a functional domain of an IAP molecule can be designed and synthesized to modulate IAP biological functions (*e.g.*, modulate apoptosis). Accordingly, in one embodiment, the invention provides a method of "rational" drug design. Another approach to "rational" drug design is based on a lead compound that is discovered using high throughput screens; the lead compound is further modified based on a crystal structure of the binding regions of the molecule in question. Accordingly, another aspect of the invention is to provide material which is a starting material in the rational design of drugs which mimic or prevent the action of an IAP (*e.g.*, a survivin molecule).

In one embodiment, a survivin monomer has an amino acid sequence as set forth in SEQ ID NO: 3. The term "amino acids" means the L-isomers of the naturally occurring amino acids or unnatural amino acids. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ-carboxyglutamic acid, arginine, ornithine and lysine. Unless specifically indicated, all amino acids referred to in this application are in the L-form.

The term "unnatural amino acids" means amino acids that are not naturally found in proteins. Examples of unnatural amino acids used herein, include racemic mixtures of selenocysteine and selenomethionine. In addition, unnatural amino acids include the D forms of amino acids, D or L forms of nor-leucine, para-nitrophenylalanine, homophenylalanine, para-fluorophenylalanine, 3-amino-2-benzylpropionic acid, homoarginine, and D-phenylalanine.

The term "crystal structure coordinates" refers to mathematical coordinates derived from mathematical equations related to the patterns obtained on diffraction of a monochromatic beam of X-rays by the atoms (scattering centers) of an IAP polypeptide (*e.g.*, a survivin protein molecule) in crystal form. The diffraction data

are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are used to establish the positions of the individual atoms within the unit cell of the crystal. The crystal structure coordinates of an IAP can be obtained from a Survivin protein crystal having space group C2 (a = 114.040 Å, b = 71.45 Å, c = 86.63, β = 133.370°). The coordinates of the survivin polypeptide can also be obtained by means of computational analysis.

The term "selenomethionine substitution" refers to the method of producing a chemically modified form of a crystal of survivin. The survivin protein is expressed by bacteria in media that is depleted in methionine and supplemented with selenomethionine. Selenium is thereby incorporated into the crystal in place of the sulfur of methionine. The location(s) of selenium are determined by X-ray diffraction analysis of the crystal. This information is used to generate the phase information used to construct a three-dimensional structure of the protein.

The term "heavy atom derivatization" refers to the method of producing a chemically modified form of a crystal of survivin. A crystal is soaked in a solution containing heavy metal atom salts or organometallic compounds, which can diffuse through the crystal and bind to the surface of the protein. The location(s) of the bound heavy metal atom(s) are determined by X-ray diffraction analysis of the soaked crystal. This information is used to generate the phase information used to construct a three-dimensional structure of the protein.

Those of skill in the art understand that a set of structure coordinates determined by X-ray crystallography is not without standard error.

The term "unit cell" refers to the basic parallelipiped shaped block. The entire volume of a crystal may be constructed by regular assembly of such blocks.

The term "space group" refers to the arrangement of symmetry elements of a crystal.

The crystal structure coordinates of the IAP polypeptide survivin can be used to design compounds that bind to the protein and alter its physical or physiological properties in a variety of ways. The structure coordinates of the protein can also be

used to computationally screen small molecule data bases for agents that bind to the polypeptide to develop IAP modulating or binding agents.

Those of skill in the art may identify binding agents or modulatory agents as inhibitors or activators by computer fitting kinetic data using standard equations according to Segel, I. H., Enzyme Kinetics, J. Wiley & Sons, (1975).

Methods of using crystal structure data to design inhibitors or binding agents are known in the art. Thus, the crystal structure data provided herein can be used in the design of new or improved inhibitors. For example, the survivin polypeptide coordinates can be superimposed onto other available coordinates of similar enzymes which have inhibitors bound to them to give an approximation of the way these and related inhibitors might bind to survivin. Alternatively, computer programs employed in the practice of rational drug design can be used to identify compounds that reproduce interaction characteristics similar to those found between a survivin polypeptide and a co-crystallized substrate. Furthermore, detailed knowledge of the nature of binding site interactions allows for the modification of compounds to alter or improve solubility, pharmacokinetics, *etc.* without affecting binding activity.

Computer programs are widely available that are capable of carrying out the activities necessary to design agents using the crystal structure information provided herein. Examples include, but are not limited to, the computer programs listed below:

Catalyst Databases™ - an information retrieval program accessing chemical databases such as BioByte Master File, Derwent WDI and ACD;

Catalyst/HYPO™ - generates models of compounds and hypotheses to explain variations of activity with the structure of drug candidates;

Ludi™ - fits molecules into the active site of a protein by identifying and matching complementary polar and hydrophobic groups;

Leapfrog™ - "grows" new ligands using a genetic algorithm with parameters under the control of the user.

In addition, various general purpose machines may be used with programs written in accordance with the teachings herein, or it may be more convenient to construct more specialized apparatus to perform the operations. However, preferably the embodiment is implemented in one or more computer programs executing on programmable systems each comprising at least one processor, at least one data storage system (including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. The program is executed on the processor to perform the functions described herein.

Each such program may be implemented in any desired computer language (including machine, assembly, high level procedural, or object oriented programming languages) to communicate with a computer system. In any case, the language may be a compiled or interpreted language. The computer program will typically be stored on a storage media or device (*e.g.*, ROM, CD-ROM, or magnetic or optical media) readable by a general or special purpose programmable computer, for configuring and operating the computer when the storage media or device is read by the computer to perform the procedures described herein. The system may also be considered to be implemented as a computer-readable storage medium, configured with a computer program, where the storage medium so configured causes a computer to operate in a specific and predefined manner to perform the functions described herein.

Embodiments of the invention include systems (*e.g.*, internet based systems), particularly computer systems which store and manipulate the coordinate and sequence information described herein. One example of a computer system 100 is illustrated in block diagram form in Figure 4. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the coordinates and sequences such as those set forth in Table 1. The computer system 100 typically includes a processor for processing, accessing and manipulating the sequence data. The processor 105 can be any well-known type of central processing unit, such as, for example, the Pentium III from Intel Corporation, or similar processor from other suppliers such as Sun, Motorola, Compaq, AMD or International Business Machines.

Typically the computer system **100** is a general purpose system that comprises the processor **105** and one or more internal data storage components **110** for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.

In one particular embodiment, the computer system **100** includes a processor **105** connected to a bus which is connected to a main memory **115** (preferably implemented as RAM) and one or more internal data storage devices **110**, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system **100** further includes one or more data retrieving device(s) **118** for reading the data stored on the internal data storage devices **110**.

The data retrieving device **118** may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, a modem capable of connection to a remote data storage system (*e.g.*, via the internet), and the like. In some embodiments, the internal data storage device **110** is a removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, and the like, containing control logic and/or data recorded thereon. The computer system **100** may advantageously include or be programmed by appropriate software for reading the control logic and/or the data from the data storage component once inserted in the data retrieving device.

The computer system **100** includes a display **120** which is used to display output to a computer user. It should also be noted that the computer system **100** can be linked to other computer systems **125a-c** in a network or wide area network to provide centralized access to the computer system **100**.

Software for accessing and processing the coordinate and sequences of Table 1, (such as search tools, compare tools, and modeling tools etc.) may reside in main memory **115** during execution.

For the first time, the present invention permits the use of molecular design techniques to design, select and synthesize chemical entities and compounds, including

inhibitory compounds, capable of binding to an IAP polypeptide (*e.g.*, a survivin polypeptide), in whole or in part.

One approach enabled by this invention, is to use the structure coordinates as set forth in Table 1 to design compounds that bind to the polypeptide and alter the physical properties of the compounds in different ways, *e.g.*, solubility. For example, the present invention enables the design of compounds that act as inhibitors of IAP biological function by binding to all, or a portion of, an IAP molecule.

In another approach a survivin polypeptide crystal is probed with a variety of different chemical entities to determine optimal sites for interaction between candidate binding molecules (*e.g.*, inhibitors) and the survivin (*i.e.*, IAP polypeptide).

In another embodiment, an approach made possible and enabled by the present invention, is to screen computationally small molecule data bases for chemical entities or compounds that can bind in whole, or in part, to an IAP polypeptide or fragment thereof. In this screening, the quality of fit of such entities or compounds to the binding site may be judged in a variety of ways, *e.g.*, by shape complementarity or by estimated interaction energy (Meng, E. C. *et al.*, J. Comp. Chem., 13:505-524, 1992).

Survivin is one member of a family of IAP polypeptides, many of which have similar functional activities. Various IAP polypeptides may crystallize in more than one crystal form. Accordingly, the structure coordinates of survivin, or portions thereof, as provided by this invention are particularly useful to solve the structure of other crystal forms of IAP molecules. They may also be used to solve the structure of an IAP or a survivin mutant.

One method that may be employed for this purpose is molecular replacement. The term "molecular replacement" refers to a method that involves generating a preliminary model of a crystal whose structure coordinates are not known, by orienting and positioning a molecule whose structure coordinates are known. Phases are then calculated from this model and combined with observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are known.

Using this method, the unknown crystal structure, whether it is another IAP crystal form, an IAP or survivin mutant, or an IAP complexed with a substrate or other molecule, or the crystal of some other protein with significant amino acid sequence homology to any IAP polypeptide, may be determined using the structure coordinates as provided in Table 1. This method will provide an accurate structural form for the unknown crystal more quickly and efficiently than attempting to determine such information *ab initio*.

TABLE 1. Atomic Coordinates

Atom	Atom Type	Res.	#	X	Y	Z	OCC	B	Molecule
1	CB	THR	5	47.044	-2.660	18.162	1.00	169.76	A
2	OG1	THR	5	47.813	-1.357	18.103	1.00	96.29	A
3	CG2	THR	5	46.544	-2.728	16.762	1.00	96.29	A
4	C	THR	5	44.906	-3.893	18.901	1.00	135.36	A
5	O	THR	5	45.129	-4.897	19.596	1.00	135.76	A
6	N	THR	5	46.120	-2.435	20.508	1.00	97.66	A
7	CA	THR	5	45.755	-2.600	19.109	1.00	128.60	A
8	N	LEU	6	43.951	-3.844	17.951	1.00	137.52	A
9	CA	LEU	6	43.072	-4.985	17.611	1.00	122.74	A
10	CB	LEU	6	41.600	-4.611	17.701	1.00	94.16	A
11	CG	LEU	6	41.143	-4.363	19.128	1.00	114.02	A
12	CD1	LEU	6	41.829	-3.113	19.778	1.00	100.92	A
13	CD2	LEU	6	39.660	-4.188	19.039	1.00	121.25	A
14	C	LEU	6	43.356	-5.470	16.198	1.00	124.46	A
15	O	LEU	6	43.928	-4.731	15.368	1.00	118.60	A
16	N	PRO	7	42.933	-6.716	15.893	1.00	107.28	A
17	CD	PRO	7	41.911	-7.510	16.602	1.00	72.47	A
18	CA	PRO	7	43.181	-7.255	14.557	1.00	114.28	A
19	CB	PRO	7	42.479	-8.621	14.575	1.00	112.46	A
20	CG	PRO	7	42.169	-8.872	16.067	1.00	82.15	A
21	C	PRO	7	42.590	-6.308	13.527	1.00	117.26	A
22	O	PRO	7	41.404	-5.993	13.550	1.00	131.06	A
23	N	PRO	8	43.407	-5.822	12.618	1.00	109.79	A
24	CD	PRO	8	44.832	-6.206	12.532	1.00	109.39	A
25	CA	PRO	8	43.035	-4.894	11.547	1.00	112.18	A
26	CB	PRO	8	44.078	-5.171	10.488	1.00	121.35	A
27	CG	PRO	8	45.335	-5.335	11.366	1.00	113.10	A
28	C	PRO	8	41.608	-4.971	10.992	1.00	108.21	A
29	O	PRO	8	40.907	-3.963	10.940	1.00	104.07	A
30	N	ALA	9	41.188	-6.163	10.585	1.00	105.13	A
31	CA	ALA	9	39.868	-6.367	10.009	1.00	83.03	A
32	CB	ALA	9	39.779	-7.757	9.393	1.00	83.43	A
33	C	ALA	9	38.732	-6.155	10.981	1.00	93.45	A

34	O	ALA	9	37.584	-6.412	10.635	1.00	101.28	A
35	N	TRP	10	39.047	-5.709	12.192	1.00	90.52	A
36	CA	TRP	10	38.027	-5.420	13.208	1.00	77.88	A
37	CB	TRP	10	38.304	-6.210	14.440	1.00	95.00	A
38	CG	TRP	10	38.067	-7.658	14.270	1.00	135.06	A
39	CD2	TRP	10	38.058	-8.614	15.324	1.00	148.77	A
40	CE2	TRP	10	37.902	-9.888	14.727	1.00	145.32	A
41	CE3	TRP	10	38.182	-8.517	16.727	1.00	142.16	A
42	CD1	TRP	10	37.907	-8.367	13.094	1.00	132.74	A
43	NE1	TRP	10	37.809	-9.706	13.369	1.00	124.82	A
44	CZ2	TRP	10	37.862	-11.062	15.496	1.00	136.92	A
45	CZ3	TRP	10	38.145	-9.673	17.481	1.00	132.92	A
46	CH2	TRP	10	37.989	-10.932	16.864	1.00	147.49	A
47	C	TRP	10	37.932	-3.924	13.609	1.00	97.19	A
48	O	TRP	10	36.933	-3.485	14.230	1.00	61.67	A
49	N	GLN	11	38.979	-3.151	13.280	1.00	56.01	A
50	CA	GLN	11	39.038	-1.702	13.580	1.00	67.17	A
51	CB	GLN	11	40.225	-1.090	12.913	1.00	60.28	A
52	CG	GLN	11	41.453	-2.029	13.117	1.00	59.09	A
53	CD	GLN	11	42.755	-1.335	12.862	1.00	92.74	A
54	OE1	GLN	11	43.023	-.289	13.474	1.00	107.00	A
55	NE2	GLN	11	43.577	-1.886	11.954	1.00	108.26	A
56	C	GLN	11	37.792	-.966	13.204	1.00	80.79	A
57	O	GLN	11	37.288	-.251	14.042	1.00	57.65	A
58	N	PRO	12	37.280	-1.126	11.955	1.00	75.96	A
59	CD	PRO	12	37.959	-1.783	10.839	1.00	70.26	A
60	CA	PRO	12	36.073	-.478	11.462	1.00	46.49	A
61	CB	PRO	12	35.715	-1.317	10.242	1.00	86.90	A
62	CG	PRO	12	36.834	-2.409	10.210	1.00	74.31	A
63	C	PRO	12	35.016	-.500	12.532	1.00	48.30	A
64	O	PRO	12	34.057	.381	12.633	1.00	62.56	A
65	N	PHE	13	35.189	-1.493	13.386	1.00	58.72	A
66	CA	PHE	13	34.207	-1.697	14.443	1.00	60.30	A
67	CB	PHE	13	34.503	-3.056	15.031	1.00	45.96	A
68	CG	PHE	13	33.559	-4.076	14.618	1.00	46.22	A
69	CD1	PHE	13	33.887	-5.061	13.646	1.00	38.31	A
70	CD2	PHE	13	32.299	-3.956	15.067	1.00	36.15	A
71	CE1	PHE	13	32.828	-5.933	13.092	1.00	51.59	A
72	CE2	PHE	13	31.308	-4.769	14.550	1.00	49.64	A
73	CZ	PHE	13	31.569	-5.761	13.551	1.00	51.47	A
74	C	PHE	13	34.359	-.631	15.511	1.00	67.94	A
75	O	PHE	13	33.495	-.364	16.334	1.00	34.08	A
76	N	LEU	14	35.539	-.073	15.529	1.00	25.96	A
77	CA	LEU	14	36.034	.948	16.480	1.00	70.16	A
78	CB	LEU	14	37.545	.742	16.628	1.00	63.17	A
79	CG	LEU	14	38.052	-.449	17.418	1.00	76.54	A
80	CD1	LEU	14	39.611	-.410	17.475	1.00	64.29	A
81	CD2	LEU	14	37.401	-.335	18.835	1.00	67.06	A
82	C	LEU	14	35.872	2.378	15.962	1.00	66.76	A
83	O	LEU	14	36.663	2.820	15.051	1.00	49.36	A
84	N	LYS	15	34.914	3.120	16.509	1.00	44.10	A

85	CA	LYS	15	34.755	4.540	16.102	1.00	76.30	A
86	CB	LYS	15	33.912	5.262	17.122	1.00	41.74	A
87	CG	LYS	15	33.785	6.797	17.022	1.00	70.13	A
88	CD	LYS	15	32.387	7.177	17.525	1.00	70.89	A
89	CE	LYS	15	32.208	8.696	17.736	1.00	92.35	A
90	NZ	LYS	15	30.814	9.190	18.303	1.00	69.70	A
91	C	LYS	15	35.958	5.419	15.832	1.00	65.43	A
92	O	LYS	15	35.998	6.092	14.813	1.00	98.59	A
93	N	ASP	16	36.939	5.403	16.716	1.00	68.18	A
94	CA	ASP	16	38.038	6.307	16.534	1.00	81.82	A
95	CB	ASP	16	38.891	6.434	17.860	1.00	52.81	A
96	CG	ASP	16	38.084	7.180	18.972	1.00	96.10	A
97	OD1	ASP	16	38.015	8.457	18.927	1.00	91.29	A
98	OD2	ASP	16	37.472	6.488	19.853	1.00	67.81	A
99	C	ASP	16	38.778	5.927	15.308	1.00	53.75	A
100	O	ASP	16	39.611	6.693	14.765	1.00	86.07	A
101	N	HIS	17	38.517	4.719	14.860	1.00	73.70	A
102	CA	HIS	17	39.152	4.212	13.652	1.00	65.88	A
103	CB	HIS	17	38.883	2.740	13.456	1.00	43.74	A
104	CG	HIS	17	39.474	2.241	12.194	1.00	47.93	A
105	CD2	HIS	17	38.908	1.906	10.998	1.00	33.73	A
106	ND1	HIS	17	40.824	2.273	11.981	1.00	45.66	A
107	CE1	HIS	17	41.079	1.987	10.702	1.00	42.01	A
108	NE2	HIS	17	39.928	1.763	10.083	1.00	83.03	A
109	C	HIS	17	38.506	4.896	12.438	1.00	88.12	A
110	O	HIS	17	39.187	5.363	11.510	1.00	37.38	A
111	N	ARG	18	37.174	4.837	12.459	1.00	30.06	A
112	CA	ARG	18	36.346	5.414	11.473	1.00	68.55	A
113	CB	ARG	18	34.980	5.279	11.908	1.00	45.35	A
114	CG	ARG	18	34.456	3.859	11.757	1.00	19.70	A
115	CD	ARG	18	32.985	3.946	12.308	1.00	38.08	A
116	NE	ARG	18	32.674	2.726	12.921	1.00	47.08	A
117	CZ	ARG	18	31.953	2.625	14.024	1.00	69.89	A
118	NH1	ARG	18	31.489	3.716	14.623	1.00	50.04	A
119	NH2	ARG	18	31.680	1.421	14.510	1.00	97.70	A
120	C	ARG	18	36.668	6.866	11.404	1.00	70.81	A
121	O	ARG	18	37.110	7.334	10.352	1.00	73.03	A
122	N	ILE	19	36.385	7.606	12.479	1.00	66.17	A
123	CA	ILE	19	36.784	9.004	12.514	1.00	46.11	A
124	CB	ILE	19	36.934	9.477	13.914	1.00	62.92	A
125	CG2	ILE	19	37.760	10.762	13.964	1.00	53.34	A
126	CG1	ILE	19	35.544	9.767	14.454	1.00	62.75	A
127	CD1	ILE	19	35.494	9.919	15.850	1.00	83.45	A
128	C	ILE	19	38.093	9.274	11.711	1.00	55.68	A
129	O	ILE	19	38.122	10.106	10.783	1.00	62.94	A
130	N	SER	20	39.107	8.457	11.976	1.00	50.75	A
131	CA	SER	20	40.430	8.586	11.389	1.00	57.24	A
132	CB	SER	20	41.422	7.580	12.105	1.00	70.98	A
133	OG	SER	20	41.540	6.277	11.480	1.00	58.70	A
134	C	SER	20	40.503	8.445	9.883	1.00	73.12	A
135	O	SER	20	41.528	8.831	9.316	1.00	62.11	A

136	N	THR	21	39.484	7.859	9.235	1.00	49.19	A
137	CA	THR	21	39.498	7.687	7.778	1.00	83.48	A
138	CB	THR	21	38.515	6.611	7.286	1.00	61.30	A
139	OG1	THR	21	37.214	6.807	7.863	1.00	57.47	A
140	CG2	THR	21	39.021	5.296	7.668	1.00	71.72	A
141	C	THR	21	39.150	9.004	7.106	1.00	97.91	A
142	O	THR	21	39.716	9.271	6.042	1.00	63.05	A
143	N	PHE	22	38.230	9.795	7.708	1.00	62.67	A
144	CA	PHE	22	37.903	11.123	7.175	1.00	58.82	A
145	CB	PHE	22	36.730	11.778	7.935	1.00	40.97	A
146	CG	PHE	22	35.503	10.906	7.929	1.00	75.54	A
147	CD1	PHE	22	35.559	9.608	8.476	1.00	52.62	A
148	CD2	PHE	22	34.312	11.355	7.369	1.00	72.93	A
149	CE1	PHE	22	34.423	8.785	8.473	1.00	83.31	A
150	CE2	PHE	22	33.160	10.546	7.355	1.00	89.30	A
151	CZ	PHE	22	33.210	9.255	7.913	1.00	62.42	A
152	C	PHE	22	39.122	12.051	7.179	1.00	72.41	A
153	O	PHE	22	39.557	12.553	8.212	1.00	88.07	A
154	N	LYS	23	39.700	12.216	6.002	1.00	98.68	A
155	CA	LYS	23	40.842	13.070	5.865	1.00	117.37	A
156	CB	LYS	23	42.143	12.270	5.664	1.00	130.82	A
157	CG	LYS	23	42.675	11.732	7.003	1.00	116.46	A
158	CD	LYS	23	44.165	11.455	7.028	1.00	119.02	A
159	CE	LYS	23	44.588	11.018	8.440	1.00	131.47	A
160	NZ	LYS	23	46.058	11.024	8.656	1.00	134.02	A
161	C	LYS	23	40.446	13.868	4.672	1.00	113.53	A
162	O	LYS	23	40.060	13.344	3.632	1.00	102.24	A
163	N	ASN	24	40.468	15.167	4.886	1.00	115.58	A
164	CA	ASN	24	40.091	16.100	3.861	1.00	92.49	A
165	CB	ASN	24	40.819	15.797	2.559	1.00	83.12	A
166	CG	ASN	24	42.269	16.263	2.604	1.00	113.95	A
167	OD1	ASN	24	43.096	15.853	1.794	1.00	122.81	A
168	ND2	ASN	24	42.581	17.132	3.568	1.00	125.73	A
169	C	ASN	24	38.610	16.044	3.706	1.00	78.34	A
170	O	ASN	24	38.083	16.359	2.663	1.00	97.05	A
171	N	TRP	25	37.928	15.607	4.749	1.00	70.05	A
172	CA	TRP	25	36.472	15.641	4.695	1.00	68.98	A
173	CB	TRP	25	35.868	14.890	5.858	1.00	40.33	A
174	CG	TRP	25	34.358	14.989	6.018	1.00	24.37	A
175	CD2	TRP	25	33.417	14.255	5.209	1.00	41.47	A
176	CE2	TRP	25	32.105	14.547	5.690	1.00	44.20	A
177	CE3	TRP	25	33.571	13.418	4.108	1.00	42.33	A
178	CD1	TRP	25	33.596	15.685	7.000	1.00	45.01	A
179	NE1	TRP	25	32.188	15.392	6.807	1.00	42.36	A
180	CZ2	TRP	25	30.970	13.944	5.105	1.00	41.16	A
181	CZ3	TRP	25	32.452	12.822	3.565	1.00	42.03	A
182	CH2	TRP	25	31.173	13.105	4.045	1.00	45.32	A
183	C	TRP	25	36.221	17.172	4.806	1.00	78.92	A
184	O	TRP	25	36.993	17.907	5.429	1.00	73.07	A
185	N	PRO	26	35.165	17.668	4.166	1.00	79.29	A
186	CD	PRO	26	34.327	16.986	3.163	1.00	79.49	A

187	CA	PRO	26	34.870	19.108	4.198	1.00	100.02	A
188	CB	PRO	26	34.379	19.368	2.780	1.00	50.86	A
189	CG	PRO	26	33.513	18.129	2.585	1.00	87.40	A
190	C	PRO	26	33.859	19.627	5.217	1.00	104.04	A
191	O	PRO	26	33.984	20.766	5.676	1.00	100.88	A
192	N	PHE	27	32.854	18.805	5.542	1.00	73.17	A
193	CA	PHE	27	31.799	19.212	6.463	1.00	91.82	A
194	CB	PHE	27	30.522	18.398	6.171	1.00	61.85	A
195	CG	PHE	27	30.126	18.463	4.706	1.00	113.66	A
196	CD1	PHE	27	30.585	17.520	3.801	1.00	99.55	A
197	CD2	PHE	27	29.442	19.569	4.206	1.00	103.81	A
198	CE1	PHE	27	30.384	17.685	2.438	1.00	113.50	A
199	CE2	PHE	27	29.242	19.730	2.846	1.00	94.53	A
200	CZ	PHE	27	29.717	18.789	1.958	1.00	92.04	A
201	C	PHE	27	32.300	19.069	7.867	1.00	90.34	A
202	O	PHE	27	32.304	17.979	8.446	1.00	97.85	A
203	N	LEU	28	32.765	20.198	8.391	1.00	80.19	A
204	CA	LEU	28	33.336	20.245	9.721	1.00	50.64	A
205	CB	LEU	28	34.761	20.748	9.664	1.00	44.01	A
206	CG	LEU	28	35.534	19.888	8.662	1.00	70.68	A
207	CD1	LEU	28	36.917	20.452	8.410	1.00	50.73	A
208	CD2	LEU	28	35.590	18.442	9.204	1.00	72.65	A
209	C	LEU	28	32.599	20.974	10.822	1.00	39.40	A
210	O	LEU	28	31.341	20.803	10.974	1.00	58.29	A
211	N	GLU	29	33.357	21.762	11.608	1.00	68.40	A
212	CA	GLU	29	32.773	22.493	12.754	1.00	62.20	A
213	CB	GLU	29	33.808	23.442	13.381	1.00	67.63	A
214	CG	GLU	29	35.283	22.959	13.338	1.00	61.60	A
215	CD	GLU	29	36.202	23.858	12.462	1.00	119.88	A
216	OE1	GLU	29	36.420	25.035	12.854	1.00	133.36	A
217	OE2	GLU	29	36.700	23.412	11.392	1.00	105.50	A
218	C	GLU	29	31.526	23.283	12.341	1.00	50.45	A
219	O	GLU	29	31.518	24.109	11.370	1.00	80.23	A
220	N	GLY	30	30.452	23.008	13.047	1.00	57.15	A
221	CA	GLY	30	29.258	23.723	12.691	1.00	40.42	A
222	C	GLY	30	28.365	22.828	11.848	1.00	69.28	A
223	O	GLY	30	27.164	22.856	12.046	1.00	48.78	A
224	N	CYS	31	28.911	22.027	10.932	1.00	70.86	A
225	CA	CYS	31	28.074	21.148	10.119	1.00	52.39	A
226	CB	CYS	31	28.938	20.569	9.064	1.00	82.67	A
227	SG	CYS	31	29.808	21.743	7.996	1.00	86.43	A
228	C	CYS	31	27.500	19.968	10.972	1.00	73.20	A
229	O	CYS	31	28.107	19.554	11.928	1.00	79.90	A
230	N	ALA	32	26.349	19.429	10.581	1.00	69.88	A
231	CA	ALA	32	25.695	18.319	11.246	1.00	59.80	A
232	CB	ALA	32	24.207	18.288	10.898	1.00	43.95	A
233	C	ALA	32	26.318	16.974	10.863	1.00	68.53	A
234	O	ALA	32	26.104	15.980	11.576	1.00	60.11	A
235	N	CYS	33	27.088	16.945	9.770	1.00	73.90	A
236	CA	CYS	33	27.710	15.722	9.302	1.00	41.29	A
237	CB	CYS	33	27.090	15.369	7.948	1.00	61.51	A

238	SG	CYS	33	27.677	16.415	6.548	1.00	80.51	A
239	C	CYS	33	29.246	15.724	9.281	1.00	54.22	A
240	O	CYS	33	29.979	15.421	8.213	1.00	52.30	A
241	N	THR	34	29.752	16.061	10.472	1.00	79.37	A
242	CA	THR	34	31.204	16.117	10.810	1.00	55.02	A
243	CB	THR	34	31.343	16.601	12.252	1.00	62.56	A
244	OG1	THR	34	30.319	15.942	13.033	1.00	64.49	A
245	CG2	THR	34	31.189	18.142	12.336	1.00	66.81	A
246	C	THR	34	31.704	14.665	10.807	1.00	46.74	A
247	O	THR	34	30.879	13.723	11.021	1.00	48.94	A
248	N	PRO	35	33.030	14.448	10.594	1.00	33.77	A
249	CD	PRO	35	34.090	15.474	10.642	1.00	39.83	A
250	CA	PRO	35	33.625	13.082	10.590	1.00	62.80	A
251	CB	PRO	35	35.128	13.363	10.674	1.00	58.30	A
252	CG	PRO	35	35.215	14.836	9.926	1.00	37.67	A
253	C	PRO	35	33.095	12.265	11.788	1.00	74.82	A
254	O	PRO	35	32.635	11.128	11.670	1.00	83.60	A
255	N	GLU	36	33.098	12.934	12.923	1.00	60.39	A
256	CA	GLU	36	32.673	12.424	14.165	1.00	64.49	A
257	CB	GLU	36	32.816	13.541	15.234	1.00	79.81	A
258	CG	GLU	36	32.786	13.078	16.725	1.00	64.48	A
259	CD	GLU	36	31.368	12.821	17.313	1.00	109.64	A
260	OE1	GLU	36	30.455	13.642	17.053	1.00	113.23	A
261	OE2	GLU	36	31.171	11.822	18.058	1.00	103.47	A
262	C	GLU	36	31.278	11.926	14.137	1.00	48.37	A
263	O	GLU	36	30.938	10.872	14.706	1.00	67.80	A
264	N	ARG	37	30.407	12.724	13.558	1.00	67.24	A
265	CA	ARG	37	29.013	12.328	13.527	1.00	62.21	A
266	CB	ARG	37	28.168	13.523	13.242	1.00	55.04	A
267	CG	ARG	37	28.032	14.450	14.450	1.00	65.57	A
268	CD	ARG	37	26.934	13.969	15.325	1.00	88.66	A
269	NE	ARG	37	25.851	13.440	14.503	1.00	111.11	A
270	CZ	ARG	37	24.582	13.385	14.924	1.00	148.16	A
271	NH1	ARG	37	24.305	13.870	16.149	1.00	110.96	A
272	NH2	ARG	37	23.605	12.774	14.196	1.00	67.32	A
273	C	ARG	37	28.730	11.258	12.495	1.00	74.31	A
274	O	ARG	37	27.756	10.538	12.621	1.00	44.18	A
275	N	MET	38	29.579	11.183	11.478	1.00	45.91	A
276	CA	MET	38	29.503	10.253	10.403	1.00	57.85	A
277	CB	MET	38	30.584	10.578	9.348	1.00	63.53	A
278	CG	MET	38	30.164	11.703	8.323	1.00	101.19	A
279	SD	MET	38	29.251	11.184	6.754	1.00	66.47	A
280	CE	MET	38	27.693	10.987	7.303	1.00	32.35	A
281	C	MET	38	29.828	8.975	11.095	1.00	67.97	A
282	O	MET	38	29.014	8.076	11.095	1.00	57.65	A
283	N	ALA	39	30.995	8.944	11.729	1.00	64.47	A
284	CA	ALA	39	31.485	7.794	12.454	1.00	50.75	A
285	CB	ALA	39	32.737	8.166	13.075	1.00	58.93	A
286	C	ALA	39	30.483	7.118	13.458	1.00	54.07	A
287	O	ALA	39	30.240	5.883	13.388	1.00	69.48	A
288	N	GLU	40	29.802	7.903	14.300	1.00	51.95	A

289	CA	GLU	40	28.892	7.251	15.219	1.00	68.44	A
290	CB	GLU	40	28.330	8.232	16.286	1.00	54.59	A
291	CG	GLU	40	27.871	9.605	15.729	1.00	121.82	A
292	CD	GLU	40	27.203	10.543	16.771	1.00	148.84	A
293	OE1	GLU	40	27.899	11.438	17.367	1.00	119.92	A
294	OE2	GLU	40	25.968	10.362	16.981	1.00	126.58	A
295	C	GLU	40	27.782	6.615	14.416	1.00	70.86	A
296	O	GLU	40	26.966	5.847	14.934	1.00	80.36	A
297	N	ALA	41	27.743	6.930	13.141	1.00	81.85	A
298	CA	ALA	41	26.659	6.423	12.348	1.00	76.17	A
299	CB	ALA	41	26.138	7.508	11.488	1.00	82.28	A
300	C	ALA	41	27.084	5.220	11.539	1.00	70.17	A
301	O	ALA	41	26.248	4.545	10.970	1.00	64.49	A
302	N	GLY	42	28.386	4.971	11.490	1.00	52.63	A
303	CA	GLY	42	28.819	3.794	10.822	1.00	52.90	A
304	C	GLY	42	29.614	3.974	9.570	1.00	79.89	A
305	O	GLY	42	30.111	2.935	9.018	1.00	52.25	A
306	N	PHE	43	29.789	5.240	9.143	1.00	60.50	A
307	CA	PHE	43	30.520	5.462	7.911	1.00	55.25	A
308	CB	PHE	43	29.978	6.699	7.121	1.00	59.52	A
309	CG	PHE	43	28.490	6.710	6.943	1.00	56.99	A
310	CD1	PHE	43	27.663	7.323	7.939	1.00	32.77	A
311	CD2	PHE	43	27.893	5.968	5.871	1.00	41.36	A
312	CE1	PHE	43	26.197	7.197	7.920	1.00	63.76	A
313	CE2	PHE	43	26.503	5.820	5.823	1.00	39.26	A
314	CZ	PHE	43	25.614	6.421	6.840	1.00	45.61	A
315	C	PHE	43	32.019	5.559	8.030	1.00	56.39	A
316	O	PHE	43	32.604	5.898	9.077	1.00	47.07	A
317	N	ILE	44	32.619	5.251	6.887	1.00	60.63	A
318	CA	ILE	44	34.035	5.262	6.658	1.00	65.91	A
319	CB	ILE	44	34.562	3.825	6.467	1.00	72.86	A
320	CG2	ILE	44	35.972	3.842	5.927	1.00	69.03	A
321	CG1	ILE	44	34.599	3.137	7.818	1.00	84.77	A
322	CD1	ILE	44	35.612	3.763	8.821	1.00	78.08	A
323	C	ILE	44	34.184	6.067	5.354	1.00	86.07	A
324	O	ILE	44	33.345	5.962	4.464	1.00	88.42	A
325	N	HIS	45	35.226	6.885	5.266	1.00	60.84	A
326	CA	HIS	45	35.458	7.683	4.084	1.00	69.10	A
327	CB	HIS	45	36.352	8.846	4.493	1.00	80.01	A
328	CG	HIS	45	36.301	9.994	3.556	1.00	94.10	A
329	CD2	HIS	45	35.258	10.585	2.925	1.00	71.19	A
330	ND1	HIS	45	37.405	10.769	3.279	1.00	92.30	A
331	CE1	HIS	45	37.048	11.791	2.540	1.00	90.20	A
332	NE2	HIS	45	35.745	11.705	2.318	1.00	89.44	A
333	C	HIS	45	36.094	6.891	2.913	1.00	65.58	A
334	O	HIS	45	37.165	6.295	3.071	1.00	84.14	A
335	N	CYS	46	35.450	6.881	1.745	1.00	74.54	A
336	CA	CYS	46	35.986	6.164	.555	1.00	98.31	A
337	CB	CYS	46	35.059	5.034	.146	1.00	103.92	A
338	SG	CYS	46	35.014	3.799	1.389	1.00	93.13	A
339	C	CYS	46	36.025	7.133	-.578	1.00	86.63	A

340	O	CYS	46	35.269	7.013	-1.521	1.00	78.16	A
341	N	PRO	47	36.921	8.103	-.511	1.00	96.10	A
342	CD	PRO	47	37.980	8.338	.479	1.00	101.90	A
343	CA	PRO	47	36.981	9.092	-1.569	1.00	111.48	A
344	CB	PRO	47	37.764	10.229	-.905	1.00	92.79	A
345	CG	PRO	47	38.767	9.482	-.128	1.00	78.59	A
346	C	PRO	47	37.549	8.652	-2.905	1.00	112.76	A
347	O	PRO	47	38.693	8.219	-2.998	1.00	116.24	A
348	N	THR	48	36.708	8.753	-3.933	1.00	122.61	A
349	CA	THR	48	37.073	8.451	-5.322	1.00	114.86	A
350	CB	THR	48	35.834	8.133	-6.226	1.00	113.59	A
351	OG1	THR	48	35.076	7.046	-5.694	1.00	93.34	A
352	CG2	THR	48	36.267	7.768	-7.618	1.00	105.31	A
353	C	THR	48	37.591	9.808	-5.832	1.00	122.56	A
354	O	THR	48	37.316	10.848	-5.218	1.00	94.69	A
355	N	GLU	49	38.326	9.820	-6.945	1.00	156.48	A
356	CA	GLU	49	38.796	11.090	-7.494	1.00	148.73	A
357	CB	GLU	49	39.786	10.875	-8.648	1.00	147.83	A
358	CG	GLU	49	40.331	12.178	-9.205	1.00	151.72	A
359	CD	GLU	49	40.642	13.190	-8.096	1.00	171.66	A
360	OE1	GLU	49	41.602	12.958	-7.320	1.00	174.47	A
361	OE2	GLU	49	39.912	14.210	-7.995	1.00	167.76	A
362	C	GLU	49	37.528	11.760	-8.002	1.00	149.65	A
363	O	GLU	49	37.394	12.986	-7.954	1.00	159.98	A
364	N	ASN	50	36.586	10.921	-8.436	1.00	108.16	A
365	CA	ASN	50	35.305	11.363	-8.957	1.00	116.15	A
366	CB	ASN	50	34.960	10.570	-10.223	1.00	154.22	A
367	CG	ASN	50	35.747	11.055	-11.431	1.00	172.02	A
368	OD1	ASN	50	36.988	11.152	-11.400	1.00	170.90	A
369	ND2	ASN	50	35.032	11.375	-12.498	1.00	158.65	A
370	C	ASN	50	34.181	11.251	-7.958	1.00	115.27	A
371	O	ASN	50	33.020	11.450	-8.313	1.00	126.21	A
372	N	GLU	51	34.538	10.963	-6.707	1.00	134.58	A
373	CA	GLU	51	33.583	10.804	-5.610	1.00	130.42	A
374	CB	GLU	51	33.108	9.367	-5.624	1.00	134.51	A
375	CG	GLU	51	32.078	9.130	-6.668	1.00	137.44	A
376	CD	GLU	51	30.774	9.857	-6.315	1.00	150.89	A
377	OE1	GLU	51	30.814	11.050	-5.883	1.00	140.08	A
378	OE2	GLU	51	29.704	9.225	-6.467	1.00	166.00	A
379	C	GLU	51	34.268	11.108	-4.288	1.00	128.61	A
380	O	GLU	51	34.483	10.208	-3.468	1.00	148.18	A
381	N	PRO	52	34.544	12.389	-4.014	1.00	95.85	A
382	CD	PRO	52	34.249	13.642	-4.677	1.00	68.40	A
383	CA	PRO	52	35.232	12.649	-2.760	1.00	98.12	A
384	CB	PRO	52	36.104	13.872	-3.108	1.00	88.72	A
385	CG	PRO	52	35.596	14.330	-4.519	1.00	90.99	A
386	C	PRO	52	34.429	12.823	-1.465	1.00	68.67	A
387	O	PRO	52	34.979	13.203	-.486	1.00	84.17	A
388	N	ASP	53	33.128	12.595	-1.473	1.00	92.94	A
389	CA	ASP	53	32.301	12.705	-.257	1.00	61.68	A
390	CB	ASP	53	31.171	13.747	-.456	1.00	99.27	A

391	CG	ASP	53	30.166	13.364	-1.616	1.00	128.56	A
392	OD1	ASP	53	30.637	13.018	-2.759	1.00	116.57	A
393	OD2	ASP	53	28.910	13.425	-1.376	1.00	86.94	A
394	C	ASP	53	31.684	11.261	-.156	1.00	87.52	A
395	O	ASP	53	30.586	11.018	.424	1.00	67.32	A
396	N	MET	54	32.394	10.309	-.761	1.00	61.27	A
397	CA	MET	54	31.945	8.928	-.763	1.00	72.05	A
398	CB	MET	54	32.768	8.151	-1.795	1.00	97.98	A
399	CG	MET	54	32.211	6.766	-2.122	1.00	75.53	A
400	SD	MET	54	30.511	6.947	-2.821	1.00	90.43	A
401	CE	MET	54	29.560	6.986	-1.358	1.00	102.57	A
402	C	MET	54	32.113	8.251	.595	1.00	93.29	A
403	O	MET	54	33.273	8.118	1.083	1.00	66.92	A
404	N	ALA	55	31.006	7.821	1.214	1.00	61.17	A
405	CA	ALA	55	31.180	7.138	2.481	1.00	77.44	A
406	CB	ALA	55	30.944	8.087	3.592	1.00	83.38	A
407	C	ALA	55	30.331	5.934	2.695	1.00	72.11	A
408	O	ALA	55	29.182	6.009	2.350	1.00	73.86	A
409	N	GLN	56	30.859	4.808	3.234	1.00	67.24	A
410	CA	GLN	56	29.949	3.666	3.540	1.00	77.64	A
411	CB	GLN	56	30.136	2.460	2.612	1.00	49.77	A
412	CG	GLN	56	31.634	2.251	2.174	1.00	43.23	A
413	CD	GLN	56	31.894	.862	1.601	1.00	39.22	A
414	OE1	GLN	56	33.099	.428	1.432	1.00	44.99	A
415	NE2	GLN	56	30.789	.111	1.291	1.00	33.32	A
416	C	GLN	56	29.967	3.059	4.917	1.00	55.98	A
417	O	GLN	56	31.041	2.956	5.483	1.00	60.49	A
418	N	CYS	57	28.799	2.639	5.378	1.00	41.09	A
419	CA	CYS	57	28.505	1.865	6.549	1.00	54.01	A
420	C	CYS	57	29.401	.662	6.477	1.00	52.12	A
421	O	CYS	57	29.225	-.121	5.526	1.00	73.61	A
422	CB	CYS	57	27.116	1.370	6.444	1.00	51.10	A
423	SG	CYS	57	26.567	.292	7.725	1.00	56.27	A
424	N	PHE	58	30.404	.582	7.383	1.00	80.51	A
425	CA	PHE	58	31.394	-.542	7.547	1.00	62.46	A
426	CB	PHE	58	32.427	-.308	8.725	1.00	58.52	A
427	CG	PHE	58	31.935	-.747	10.060	1.00	39.42	A
428	CD1	PHE	58	32.324	-2.003	10.571	1.00	53.99	A
429	CD2	PHE	58	30.913	-.052	10.766	1.00	22.12	A
430	CE1	PHE	58	31.673	-2.531	11.704	1.00	36.25	A
431	CE2	PHE	58	30.216	-.536	11.935	1.00	54.70	A
432	CZ	PHE	58	30.582	-1.795	12.414	1.00	35.73	A
433	C	PHE	58	30.664	-1.956	7.730	1.00	54.02	A
434	O	PHE	58	31.242	-3.003	7.352	1.00	45.93	A
435	N	PHE	59	29.457	-1.971	8.266	1.00	40.58	A
436	CA	PHE	59	28.620	-3.138	8.444	1.00	63.83	A
437	CB	PHE	59	27.695	-2.764	9.576	1.00	52.94	A
438	CG	PHE	59	27.213	-3.894	10.327	1.00	64.04	A
439	CD1	PHE	59	28.114	-4.619	11.102	1.00	74.68	A
440	CD2	PHE	59	25.846	-4.261	10.285	1.00	81.98	A
441	CE1	PHE	59	27.703	-5.717	11.849	1.00	59.37	A

442	CE2	PHE	59	25.383	-5.360	11.013	1.00	70.60	A
443	CZ	PHE	59	26.323	-6.105	11.812	1.00	85.16	A
444	C	PHE	59	27.826	-3.568	7.115	1.00	93.56	A
445	O	PHE	59	28.222	-4.528	6.439	1.00	86.12	A
446	N	CYS	60	26.747	-2.859	6.789	1.00	112.16	A
447	CA	CYS	60	25.786	-2.967	5.643	1.00	65.89	A
448	C	CYS	60	26.374	-2.143	4.581	1.00	66.31	A
449	O	CYS	60	25.832	-1.004	4.475	1.00	78.18	A
450	CB	CYS	60	24.588	-2.096	6.040	1.00	65.86	A
451	SG	CYS	60	24.778	-.475	7.094	1.00	88.33	A
452	N	PHE	61	27.353	-2.643	3.822	1.00	43.05	A
453	CA	PHE	61	28.173	-1.815	2.892	1.00	56.46	A
454	CB	PHE	61	29.119	-2.706	2.185	1.00	58.92	A
455	CG	PHE	61	29.946	-3.478	3.090	1.00	63.90	A
456	CD1	PHE	61	29.368	-4.451	3.972	1.00	46.83	A
457	CD2	PHE	61	31.309	-3.285	3.045	1.00	52.47	A
458	CE1	PHE	61	30.174	-5.176	4.742	1.00	45.09	A
459	CE2	PHE	61	32.155	-4.027	3.816	1.00	56.31	A
460	CZ	PHE	61	31.603	-4.964	4.679	1.00	48.56	A
461	C	PHE	61	27.721	-.701	1.938	1.00	69.26	A
462	O	PHE	61	28.465	-.276	1.016	1.00	52.79	A
463	N	LYS	62	26.551	-.153	2.254	1.00	50.03	A
464	CA	LYS	62	25.974	.965	1.565	1.00	56.05	A
465	CB	LYS	62	24.711	1.470	2.233	1.00	47.81	A
466	CG	LYS	62	24.111	2.609	1.377	1.00	65.05	A
467	CD	LYS	62	22.602	2.649	1.512	1.00	82.42	A
468	CE	LYS	62	21.893	1.423	.905	1.00	103.60	A
469	NZ	LYS	62	21.808	1.388	-.587	1.00	86.88	A
470	C	LYS	62	26.871	2.144	1.446	1.00	69.48	A
471	O	LYS	62	27.543	2.545	2.420	1.00	71.12	A
472	N	GLU	63	26.847	2.713	.237	1.00	70.89	A
473	CA	GLU	63	27.620	3.900	-.031	1.00	57.95	A
474	CB	GLU	63	28.544	3.620	-1.154	1.00	58.60	A
475	CG	GLU	63	29.265	2.258	-.978	1.00	53.57	A
476	CD	GLU	63	30.497	2.194	-1.874	1.00	80.22	A
477	OE1	GLU	63	31.468	2.990	-1.635	1.00	92.51	A
478	OE2	GLU	63	30.474	1.366	-2.820	1.00	96.53	A
479	C	GLU	63	26.716	5.110	-.248	1.00	71.29	A
480	O	GLU	63	25.528	4.964	-.508	1.00	66.93	A
481	N	LEU	64	27.245	6.303	.004	1.00	80.00	A
482	CA	LEU	64	26.434	7.525	-.150	1.00	77.41	A
483	CB	LEU	64	25.681	7.841	1.103	1.00	45.59	A
484	CG	LEU	64	24.695	6.794	1.615	1.00	70.00	A
485	CD1	LEU	64	24.032	7.215	2.916	1.00	49.60	A
486	CD2	LEU	64	23.604	6.599	.618	1.00	61.67	A
487	C	LEU	64	27.229	8.751	-.498	1.00	72.03	A
488	O	LEU	64	28.359	8.961	.012	1.00	96.70	A
489	N	GLU	65	26.661	9.571	-1.382	1.00	94.43	A
490	CA	GLU	65	27.330	10.825	-1.754	1.00	50.43	A
491	CB	GLU	65	27.871	10.763	-3.191	1.00	98.90	A
492	CG	GLU	65	27.567	9.453	-3.892	1.00	129.15	A

493	CD	GLU	65	26.678	9.624	-5.102	1.00	150.49	A
494	OE1	GLU	65	27.144	10.235	-6.071	1.00	141.84	A
495	OE2	GLU	65	25.525	9.156	-5.092	1.00	152.41	A
496	C	GLU	65	26.265	11.867	-1.611	1.00	75.79	A
497	O	GLU	65	25.091	11.485	-1.247	1.00	69.97	A
498	N	GLY	66	26.673	13.140	-1.834	1.00	71.85	A
499	CA	GLY	66	25.763	14.281	-1.805	1.00	70.91	A
500	C	GLY	66	25.535	14.844	-.429	1.00	88.88	A
501	O	GLY	66	24.386	15.137	-.045	1.00	70.49	A
502	N	TRP	67	26.632	15.054	.290	1.00	85.06	A
503	CA	TRP	67	26.547	15.490	1.677	1.00	91.46	A
504	CB	TRP	67	27.796	14.970	2.455	1.00	110.78	A
505	CG	TRP	67	27.822	13.423	2.718	1.00	75.82	A
506	CD2	TRP	67	26.902	12.686	3.554	1.00	62.94	A
507	CE2	TRP	67	27.131	11.319	3.372	1.00	47.12	A
508	CE3	TRP	67	25.920	13.050	4.496	1.00	55.77	A
509	CD1	TRP	67	28.570	12.462	2.042	1.00	74.25	A
510	NE1	TRP	67	28.150	11.204	2.404	1.00	71.77	A
511	CZ2	TRP	67	26.407	10.321	4.004	1.00	62.26	A
512	CZ3	TRP	67	25.180	12.057	5.131	1.00	77.54	A
513	CH2	TRP	67	25.449	10.719	4.898	1.00	71.53	A
514	C	TRP	67	26.432	16.985	1.821	1.00	85.87	A
515	O	TRP	67	27.280	17.688	1.317	1.00	91.10	A
516	N	GLU	68	25.405	17.448	2.531	1.00	91.21	A
517	CA	GLU	68	25.156	18.876	2.801	1.00	81.88	A
518	CB	GLU	68	23.703	19.261	2.523	1.00	99.28	A
519	CG	GLU	68	23.085	18.556	1.365	1.00	113.26	A
520	CD	GLU	68	21.888	19.280	.833	1.00	100.11	A
521	OE1	GLU	68	20.860	19.426	1.576	1.00	90.26	A
522	OE2	GLU	68	22.024	19.695	-.344	1.00	87.17	A
523	C	GLU	68	25.348	19.103	4.283	1.00	73.89	A
524	O	GLU	68	24.792	18.369	5.091	1.00	70.75	A
525	N	PRO	69	26.046	20.170	4.670	1.00	86.26	A
526	CD	PRO	69	26.471	21.228	3.744	1.00	99.78	A
527	CA	PRO	69	26.345	20.555	6.068	1.00	72.59	A
528	CB	PRO	69	26.707	22.020	5.925	1.00	97.36	A
529	CG	PRO	69	27.438	22.045	4.607	1.00	51.92	A
530	C	PRO	69	25.235	20.344	7.099	1.00	48.43	A
531	O	PRO	69	25.442	20.350	8.327	1.00	105.72	A
532	N	ASP	70	24.042	20.163	6.570	1.00	70.31	A
533	CA	ASP	70	22.855	20.056	7.362	1.00	60.36	A
534	CB	ASP	70	21.792	20.961	6.698	1.00	93.64	A
535	CG	ASP	70	21.117	21.885	7.686	1.00	114.92	A
536	OD1	ASP	70	20.164	21.423	8.359	1.00	115.57	A
537	OD2	ASP	70	21.548	23.054	7.793	1.00	104.94	A
538	C	ASP	70	22.354	18.665	7.591	1.00	69.17	A
539	O	ASP	70	21.419	18.454	8.376	1.00	65.98	A
540	N	ASP	71	23.002	17.741	6.895	1.00	69.61	A
541	CA	ASP	71	22.714	16.301	6.936	1.00	83.31	A
542	CB	ASP	71	23.404	15.598	5.742	1.00	87.32	A
543	CG	ASP	71	22.714	15.851	4.397	1.00	112.98	A

544	OD1	ASP	71	21.559	16.340	4.437	1.00	87.99	A
545	OD2	ASP	71	23.319	15.538	3.311	1.00	78.89	A
546	C	ASP	71	23.143	15.529	8.217	1.00	72.58	A
547	O	ASP	71	24.331	15.439	8.576	1.00	66.34	A
548	N	ASP	72	22.149	14.958	8.855	1.00	61.45	A
549	CA	ASP	72	22.255	14.057	9.997	1.00	66.01	A
550	CB	ASP	72	20.851	14.003	10.669	1.00	58.63	A
551	CG	ASP	72	20.824	13.041	11.877	1.00	95.41	A
552	OD1	ASP	72	21.836	12.318	12.069	1.00	67.12	A
553	OD2	ASP	72	19.826	12.971	12.632	1.00	70.05	A
554	C	ASP	72	22.666	12.585	9.447	1.00	74.78	A
555	O	ASP	72	21.833	11.834	8.908	1.00	42.83	A
556	N	PRO	73	23.935	12.167	9.595	1.00	46.80	A
557	CD	PRO	73	25.112	12.799	10.255	1.00	77.88	A
558	CA	PRO	73	24.262	10.842	9.068	1.00	43.07	A
559	CB	PRO	73	25.744	10.690	9.393	1.00	53.32	A
560	CG	PRO	73	26.281	12.100	9.567	1.00	52.61	A
561	C	PRO	73	23.422	9.664	9.593	1.00	42.91	A
562	O	PRO	73	23.375	8.610	8.993	1.00	78.59	A
563	N	ILE	74	22.801	9.833	10.736	1.00	61.96	A
564	CA	ILE	74	22.043	8.772	11.277	1.00	52.05	A
565	CB	ILE	74	21.858	9.002	12.765	1.00	71.50	A
566	CG2	ILE	74	20.802	8.124	13.352	1.00	47.49	A
567	CG1	ILE	74	23.192	8.669	13.449	1.00	78.43	A
568	CD1	ILE	74	23.328	9.189	14.939	1.00	77.08	A
569	C	ILE	74	20.759	8.571	10.499	1.00	80.08	A
570	O	ILE	74	20.712	7.654	9.660	1.00	77.48	A
571	N	GLU	75	19.743	9.413	10.729	1.00	81.62	A
572	CA	GLU	75	18.453	9.294	10.009	1.00	97.81	A
573	CB	GLU	75	17.499	10.477	10.353	1.00	55.86	A
574	CG	GLU	75	16.080	9.983	10.863	1.00	130.63	A
575	CD	GLU	75	16.062	9.521	12.363	1.00	123.19	A
576	OE1	GLU	75	17.139	9.472	12.989	1.00	128.11	A
577	OE2	GLU	75	14.979	9.209	12.924	1.00	122.57	A
578	C	GLU	75	18.615	9.107	8.468	1.00	89.74	A
579	O	GLU	75	17.726	8.533	7.845	1.00	69.08	A
580	N	GLU	76	19.731	9.585	7.887	1.00	50.72	A
581	CA	GLU	76	20.056	9.348	6.462	1.00	60.90	A
582	CB	GLU	76	21.446	9.916	6.088	1.00	46.91	A
583	CG	GLU	76	21.503	11.310	5.516	1.00	101.78	A
584	CD	GLU	76	20.573	11.461	4.345	1.00	107.41	A
585	OE1	GLU	76	21.040	11.323	3.164	1.00	76.79	A
586	OE2	GLU	76	19.361	11.692	4.626	1.00	79.04	A
587	C	GLU	76	20.141	7.812	6.266	1.00	89.15	A
588	O	GLU	76	19.433	7.185	5.474	1.00	81.89	A
589	N	HIS	77	21.081	7.239	6.999	1.00	109.36	A
590	CA	HIS	77	21.346	5.812	7.050	1.00	76.85	A
591	CB	HIS	77	22.291	5.603	8.221	1.00	92.70	A
592	CG	HIS	77	22.949	4.268	8.288	1.00	88.62	A
593	CD2	HIS	77	22.642	3.056	7.763	1.00	62.76	A
594	ND1	HIS	77	24.182	4.125	8.878	1.00	88.24	A

595	CE1	HIS	77	24.622	2.907	8.686	1.00	69.04	A
596	NE2	HIS	77	23.704	2.235	8.012	1.00	97.72	A
597	C	HIS	77	20.054	4.970	7.259	1.00	82.81	A
598	O	HIS	77	19.868	3.958	6.591	1.00	73.67	A
599	N	LYS	78	19.185	5.362	8.198	1.00	68.20	A
600	CA	LYS	78	17.959	4.600	8.451	1.00	72.64	A
601	CB	LYS	78	17.196	5.138	9.678	1.00	83.34	A
602	CG	LYS	78	18.004	5.368	10.965	1.00	103.13	A
603	CD	LYS	78	17.102	6.047	11.986	1.00	100.27	A
604	CE	LYS	78	17.352	5.625	13.421	1.00	103.92	A
605	NZ	LYS	78	16.242	6.143	14.283	1.00	91.56	A
606	C	LYS	78	17.025	4.731	7.272	1.00	86.20	A
607	O	LYS	78	16.054	4.008	7.154	1.00	83.68	A
608	N	LYS	79	17.299	5.695	6.418	1.00	96.63	A
609	CA	LYS	79	16.443	5.964	5.290	1.00	84.92	A
610	CB	LYS	79	16.636	7.426	4.844	1.00	94.91	A
611	CG	LYS	79	15.800	7.868	3.678	1.00	88.48	A
612	CD	LYS	79	16.003	9.306	3.395	1.00	105.52	A
613	CE	LYS	79	15.211	9.723	2.170	1.00	97.12	A
614	NZ	LYS	79	15.950	10.825	1.467	1.00	67.32	A
615	C	LYS	79	16.884	5.011	4.214	1.00	78.60	A
616	O	LYS	79	16.155	4.117	3.802	1.00	93.95	A
617	N	HIS	80	18.117	5.187	3.798	1.00	54.25	A
618	CA	HIS	80	18.694	4.361	2.757	1.00	57.93	A
619	CB	HIS	80	19.842	5.130	2.072	1.00	65.38	A
620	CG	HIS	80	19.425	6.454	1.518	1.00	107.72	A
621	CD2	HIS	80	18.243	7.111	1.582	1.00	92.34	A
622	ND1	HIS	80	20.294	7.289	.861	1.00	104.21	A
623	CE1	HIS	80	19.670	8.412	.547	1.00	107.30	A
624	NE2	HIS	80	18.425	8.327	.976	1.00	120.26	A
625	C	HIS	80	19.198	2.937	3.112	1.00	90.23	A
626	O	HIS	80	19.792	2.277	2.249	1.00	102.23	A
627	N	SER	81	18.990	2.463	4.350	1.00	89.57	A
628	CA	SER	81	19.442	1.117	4.762	1.00	60.61	A
629	CB	SER	81	20.966	1.030	4.959	1.00	59.10	A
630	OG	SER	81	21.466	-.303	5.080	1.00	71.12	A
631	C	SER	81	18.756	.610	6.003	1.00	71.37	A
632	O	SER	81	19.339	-.128	6.767	1.00	74.66	A
633	N	SER	82	17.497	.985	6.166	1.00	91.81	A
634	CA	SER	82	16.695	.578	7.309	1.00	78.36	A
635	CB	SER	82	15.214	.582	6.890	1.00	94.84	A
636	OG	SER	82	14.383	.303	7.998	1.00	106.90	A
637	C	SER	82	17.075	-.767	7.974	1.00	93.40	A
638	O	SER	82	16.991	-.909	9.203	1.00	102.54	A
639	N	GLY	83	17.501	-1.745	7.175	1.00	91.29	A
640	CA	GLY	83	17.856	-3.039	7.747	1.00	81.43	A
641	C	GLY	83	19.320	-3.283	8.087	1.00	78.12	A
642	O	GLY	83	19.864	-4.379	7.897	1.00	96.08	A
643	N	CYS	84	19.987	-2.235	8.557	1.00	113.86	A
644	CA	CYS	84	21.394	-2.368	8.949	1.00	94.49	A
645	C	CYS	84	21.280	-2.735	10.403	1.00	100.59	A

646	O	CYS	84	20.522	-2.116	11.181	1.00	89.55	A
647	CB	CYS	84	22.147	-1.058	8.824	1.00	63.85	A
648	SG	CYS	84	23.934	-1.137	8.914	1.00	68.65	A
649	N	ALA	85	22.021	-3.774	10.756	1.00	87.80	A
650	CA	ALA	85	22.002	-4.262	12.111	1.00	97.09	A
651	CB	ALA	85	22.650	-5.574	12.165	1.00	75.95	A
652	C	ALA	85	22.718	-3.267	13.020	1.00	95.03	A
653	O	ALA	85	22.278	-3.009	14.146	1.00	68.61	A
654	N	PHE	86	23.830	-2.716	12.541	1.00	61.52	A
655	CA	PHE	86	24.526	-1.723	13.313	1.00	58.28	A
656	CB	PHE	86	25.379	-.886	12.441	1.00	42.44	A
657	CG	PHE	86	26.363	-.030	13.179	1.00	76.81	A
658	CD1	PHE	86	27.568	-.522	13.591	1.00	75.78	A
659	CD2	PHE	86	26.066	1.283	13.460	1.00	98.40	A
660	CE1	PHE	86	28.460	.306	14.298	1.00	85.92	A
661	CE2	PHE	86	26.942	2.092	14.144	1.00	73.36	A
662	CZ	PHE	86	28.144	1.600	14.563	1.00	87.67	A
663	C	PHE	86	23.601	-.781	14.004	1.00	66.73	A
664	O	PHE	86	23.734	-.503	15.188	1.00	84.96	A
665	N	LEU	87	22.678	-.257	13.227	1.00	69.46	A
666	CA	LEU	87	21.755	.719	13.765	1.00	64.20	A
667	CB	LEU	87	20.741	1.216	12.722	1.00	65.05	A
668	CG	LEU	87	21.194	1.462	11.282	1.00	88.69	A
669	CD1	LEU	87	20.145	2.301	10.581	1.00	85.87	A
670	CD2	LEU	87	22.557	2.152	11.228	1.00	53.57	A
671	C	LEU	87	20.994	.260	14.956	1.00	85.50	A
672	O	LEU	87	20.496	1.110	15.675	1.00	87.14	A
673	N	SER	88	20.861	-1.042	15.201	1.00	89.42	A
674	CA	SER	88	20.077	-1.409	16.388	1.00	86.66	A
675	CB	SER	88	19.083	-2.565	16.100	1.00	71.26	A
676	OG	SER	88	19.636	-3.583	15.287	1.00	112.57	A
677	C	SER	88	20.980	-1.667	17.603	1.00	82.75	A
678	O	SER	88	20.509	-1.813	18.714	1.00	74.63	A
679	N	VAL	89	22.281	-1.551	17.370	1.00	58.83	A
680	CA	VAL	89	23.352	-1.729	18.317	1.00	54.49	A
681	CB	VAL	89	24.606	-2.044	17.514	1.00	77.36	A
682	CG1	VAL	89	25.902	-1.673	18.239	1.00	57.79	A
683	CG2	VAL	89	24.539	-3.494	17.189	1.00	62.13	A
684	C	VAL	89	23.549	-.558	19.259	1.00	87.54	A
685	O	VAL	89	24.297	.396	18.982	1.00	84.47	A
686	N	LYS	90	22.893	-.653	20.406	1.00	96.07	A
687	CA	LYS	90	22.952	.405	21.403	1.00	98.32	A
688	CB	LYS	90	21.512	.711	21.824	1.00	91.17	A
689	CG	LYS	90	20.671	-.566	21.916	1.00	100.72	A
690	CD	LYS	90	19.247	-.358	22.407	1.00	125.87	A
691	CE	LYS	90	18.718	-1.662	23.044	1.00	129.61	A
692	NZ	LYS	90	17.551	-1.466	23.964	1.00	103.53	A
693	C	LYS	90	23.823	.054	22.614	1.00	95.01	A
694	O	LYS	90	23.310	-.117	23.691	1.00	105.59	A
695	N	LYS	91	25.133	-.080	22.437	1.00	76.84	A
696	CA	LYS	91	26.079	-.415	23.521	1.00	71.97	A

697	CB	LYS	91	26.148	-1.931	23.859	1.00	59.78	A
698	CG	LYS	91	24.964	-2.510	24.657	1.00	71.75	A
699	CD	LYS	91	25.187	-4.016	24.936	1.00	63.37	A
700	CE	LYS	91	24.022	-4.643	25.628	1.00	79.73	A
701	NZ	LYS	91	24.379	-5.955	26.137	1.00	88.49	A
702	C	LYS	91	27.423	-.020	22.969	1.00	70.19	A
703	O	LYS	91	27.650	-.083	21.742	1.00	81.43	A
704	N	GLN	92	28.336	.403	23.834	1.00	77.22	A
705	CA	GLN	92	29.603	.754	23.269	1.00	87.83	A
706	CB	GLN	92	30.412	1.693	24.165	1.00	127.19	A
707	CG	GLN	92	30.181	3.191	23.831	1.00	123.16	A
708	CD	GLN	92	30.646	3.605	22.402	1.00	141.54	A
709	OE1	GLN	92	30.097	3.144	21.389	1.00	130.00	A
710	NE2	GLN	92	31.659	4.480	22.334	1.00	131.63	A
711	C	GLN	92	30.313	-.538	22.986	1.00	88.23	A
712	O	GLN	92	29.888	-1.640	23.412	1.00	82.54	A
713	N	PHE	93	31.367	-.417	22.195	1.00	87.13	A
714	CA	PHE	93	32.126	-1.586	21.815	1.00	71.89	A
715	CB	PHE	93	33.394	-1.116	21.115	1.00	65.03	A
716	CG	PHE	93	34.091	-2.179	20.385	1.00	65.68	A
717	CD1	PHE	93	33.383	-3.047	19.577	1.00	67.27	A
718	CD2	PHE	93	35.456	-2.330	20.502	1.00	95.48	A
719	CE1	PHE	93	34.056	-4.072	18.891	1.00	63.92	A
720	CE2	PHE	93	36.123	-3.339	19.826	1.00	91.93	A
721	CZ	PHE	93	35.425	-4.208	19.018	1.00	81.49	A
722	C	PHE	93	32.446	-2.524	23.018	1.00	101.89	A
723	O	PHE	93	31.886	-3.621	23.125	1.00	88.08	A
724	N	GLU	94	33.302	-2.065	23.934	1.00	108.35	A
725	CA	GLU	94	33.728	-2.880	25.072	1.00	72.93	A
726	CB	GLU	94	34.682	-2.103	25.935	1.00	70.78	A
727	CG	GLU	94	35.461	-1.123	25.154	1.00	110.30	A
728	CD	GLU	94	36.945	-1.258	25.355	1.00	103.21	A
729	OE1	GLU	94	37.457	-.954	26.462	1.00	98.21	A
730	OE2	GLU	94	37.610	-1.664	24.383	1.00	121.36	A
731	C	GLU	94	32.638	-3.455	25.943	1.00	70.01	A
732	O	GLU	94	32.872	-4.387	26.709	1.00	84.91	A
733	N	GLU	95	31.432	-2.956	25.787	1.00	57.38	A
734	CA	GLU	95	30.352	-3.427	26.624	1.00	63.04	A
735	CB	GLU	95	29.412	-2.253	26.787	1.00	58.01	A
736	CG	GLU	95	28.385	-2.274	27.890	1.00	124.74	A
737	CD	GLU	95	27.485	-1.024	27.824	1.00	141.28	A
738	OE1	GLU	95	28.043	.086	27.565	1.00	104.27	A
739	OE2	GLU	95	26.246	-1.163	28.029	1.00	121.36	A
740	C	GLU	95	29.647	-4.640	26.064	1.00	64.32	A
741	O	GLU	95	28.658	-5.151	26.621	1.00	81.23	A
742	N	LEU	96	30.149	-5.121	24.946	1.00	88.06	A
743	CA	LEU	96	29.551	-6.259	24.290	1.00	79.92	A
744	CB	LEU	96	29.709	-6.073	22.788	1.00	103.70	A
745	CG	LEU	96	28.843	-5.220	21.872	1.00	81.22	A
746	CD1	LEU	96	29.527	-5.281	20.603	1.00	52.56	A
747	CD2	LEU	96	27.450	-5.801	21.636	1.00	49.59	A

748	C	LEU	96	30.166	-7.604	24.670	1.00	83.23	A
749	O	LEU	96	31.366	-7.692	24.917	1.00	63.37	A
750	N	THR	97	29.349	-8.652	24.680	1.00	74.70	A
751	CA	THR	97	29.837	-10.026	24.927	1.00	70.11	A
752	CB	THR	97	28.689	-10.965	25.074	1.00	60.65	A
753	OG1	THR	97	27.713	-10.370	25.914	1.00	96.54	A
754	CG2	THR	97	29.115	-12.228	25.679	1.00	89.80	A
755	C	THR	97	30.557	-10.522	23.673	1.00	66.18	A
756	O	THR	97	29.959	-10.418	22.598	1.00	100.92	A
757	N	LEU	98	31.778	-11.073	23.777	1.00	80.37	A
758	CA	LEU	98	32.437	-11.606	22.577	1.00	68.53	A
759	CB	LEU	98	33.549	-12.581	22.904	1.00	47.56	A
760	CG	LEU	98	34.824	-12.118	23.637	1.00	62.91	A
761	CD1	LEU	98	35.910	-11.617	22.763	1.00	62.53	A
762	CD2	LEU	98	34.391	-11.052	24.619	1.00	73.53	A
763	C	LEU	98	31.402	-12.399	21.763	1.00	84.94	A
764	O	LEU	98	31.524	-12.531	20.550	1.00	81.86	A
765	N	GLY	99	30.405	-12.964	22.434	1.00	75.32	A
766	CA	GLY	99	29.355	-13.667	21.726	1.00	65.35	A
767	C	GLY	99	28.681	-12.631	20.839	1.00	85.81	A
768	O	GLY	99	28.878	-12.603	19.612	1.00	63.18	A
769	N	GLU	100	27.914	-11.748	21.477	1.00	75.10	A
770	CA	GLU	100	27.207	-10.692	20.758	1.00	90.61	A
771	CB	GLU	100	26.935	-9.588	21.762	1.00	55.26	A
772	CG	GLU	100	25.765	-9.884	22.635	1.00	68.28	A
773	CD	GLU	100	25.618	-8.932	23.851	1.00	97.04	A
774	OE1	GLU	100	26.570	-8.165	24.232	1.00	82.89	A
775	OE2	GLU	100	24.513	-8.980	24.452	1.00	89.69	A
776	C	GLU	100	27.993	-10.137	19.537	1.00	70.05	A
777	O	GLU	100	27.501	-9.972	18.411	1.00	77.86	A
778	N	PHE	101	29.258	-9.889	19.781	1.00	56.69	A
779	CA	PHE	101	30.157	-9.342	18.807	1.00	52.87	A
780	CB	PHE	101	31.471	-8.955	19.542	1.00	34.54	A
781	CG	PHE	101	32.564	-8.605	18.634	1.00	48.55	A
782	CD1	PHE	101	32.613	-7.321	18.070	1.00	58.53	A
783	CD2	PHE	101	33.546	-9.525	18.308	1.00	53.21	A
784	CE1	PHE	101	33.662	-6.920	17.168	1.00	50.86	A
785	CE2	PHE	101	34.607	-9.188	17.422	1.00	64.70	A
786	CZ	PHE	101	34.658	-7.830	16.835	1.00	55.55	A
787	C	PHE	101	30.477	-10.265	17.651	1.00	53.91	A
788	O	PHE	101	30.444	-9.863	16.499	1.00	92.64	A
789	N	LEU	102	30.881	-11.490	17.984	1.00	84.07	A
790	CA	LEU	102	31.260	-12.478	16.970	1.00	69.29	A
791	CB	LEU	102	31.779	-13.750	17.607	1.00	78.54	A
792	CG	LEU	102	33.240	-13.596	18.000	1.00	75.94	A
793	CD1	LEU	102	33.623	-14.780	18.778	1.00	69.55	A
794	CD2	LEU	102	34.133	-13.414	16.806	1.00	61.90	A
795	C	LEU	102	30.047	-12.798	16.030	1.00	80.99	A
796	O	LEU	102	30.240	-13.140	14.903	1.00	52.50	A
797	N	LYS	103	28.901	-12.759	16.541	1.00	43.62	A
798	CA	LYS	103	27.653	-12.865	15.780	1.00	50.45	A

799	CB	LYS	103	26.461	-12.793	16.751	1.00	42.71	A
800	CG	LYS	103	25.165	-12.984	16.095	1.00	82.77	A
801	CD	LYS	103	24.101	-13.033	17.177	1.00	85.40	A
802	CE	LYS	103	22.909	-13.903	16.796	1.00	90.63	A
803	NZ	LYS	103	23.158	-14.566	15.509	1.00	108.92	A
804	C	LYS	103	27.580	-11.680	14.728	1.00	84.13	A
805	O	LYS	103	27.384	-11.909	13.526	1.00	102.24	A
806	N	LEU	104	27.781	-10.443	15.178	1.00	82.20	A
807	CA	LEU	104	27.737	-9.315	14.250	1.00	59.21	A
808	CB	LEU	104	27.774	-7.960	14.989	1.00	59.76	A
809	CG	LEU	104	26.687	-7.753	16.045	1.00	66.37	A
810	CD1	LEU	104	27.099	-6.546	16.709	1.00	59.66	A
811	CD2	LEU	104	25.279	-7.607	15.480	1.00	81.99	A
812	C	LEU	104	28.905	-9.378	13.306	1.00	56.77	A
813	O	LEU	104	28.827	-8.900	12.163	1.00	91.16	A
814	N	ASP	105	30.011	-9.954	13.728	1.00	55.72	A
815	CA	ASP	105	31.040	-9.897	12.726	1.00	58.54	A
816	CB	ASP	105	32.427	-10.213	13.239	1.00	40.52	A
817	CG	ASP	105	33.440	-9.658	12.323	1.00	68.17	A
818	OD1	ASP	105	33.089	-8.561	11.807	1.00	109.67	A
819	OD2	ASP	105	34.548	-10.223	12.105	1.00	66.05	A
820	C	ASP	105	30.668	-10.879	11.659	1.00	64.54	A
821	O	ASP	105	31.293	-10.956	10.613	1.00	65.87	A
822	N	ARG	106	29.645	-11.658	11.970	1.00	66.07	A
823	CA	ARG	106	29.126	-12.636	11.059	1.00	80.68	A
824	CB	ARG	106	28.534	-13.832	11.795	1.00	70.31	A
825	CG	ARG	106	29.704	-14.804	12.140	1.00	75.92	A
826	CD	ARG	106	29.305	-16.196	12.617	1,00	78.14	A
827	NE	ARG	106	28.270	-16.230	13.696	1.00	91.27	A
828	CZ	ARG	106	28.529	-16.291	15.021	1.00	93.35	A
829	NH1	ARG	106	29.808	-16.333	15.461	1.00	50.84	A
830	NH2	ARG	106	27.537	-16.336	15.932	1.00	61.41	A
831	C	ARG	106	28.179	-11.939	10.133	1.00	90.29	A
832	O	ARG	106	28.444	-12.053	8.951	1.00	73.07	A
833	N	GLU	107	27.121	-11.233	10.577	1.00	64.23	A
834	CA	GLU	107	26.354	-10.508	9.532	1.00	66.58	A
835	CB	GLU	107	25.369	-9.550	10.099	1.00	52.46	A
836	CG	GLU	107	24.191	-10.144	10.883	1.00	73.39	A
837	CD	GLU	107	22.986	-9.165	10.932	1.00	66.88	A
838	OE1	GLU	107	22.794	-8.436	9.919	1.00	115.67	A
839	OE2	GLU	107	22.219	-9.137	11.951	1.00	99.98	A
840	C	GLU	107	27.268	-9.660	8.591	1.00	63.22	A
841	O	GLU	107	27.191	-9.738	7.359	1.00	91.98	A
842	N	ARG	108	28.137	-8.852	9.178	1.00	49.45	A
843	CA	ARG	108	29.029	-8.050	8.392	1.00	66.88	A
844	CB	ARG	108	30.237	-7.505	9.218	1.00	50.45	A
845	CG	ARG	108	30.647	-6.116	8.888	1.00	68.77	A
846	CD	ARG	108	32.134	-5.910	8.551	1.00	52.88	A
847	NE	ARG	108	32.994	-6.455	9.567	1.00	68.58	A
848	CZ	ARG	108	34.296	-6.222	9.639	1.00	89.78	A
849	NH1	ARG	108	34.870	-5.416	8.775	1.00	61.96	A

850	NH2	ARG	108	35.047	-6.905	10.489	1.00	72.57	A
851	C	ARG	108	29.587	-8.900	7.239	1.00	61.03	A
852	O	ARG	108	29.380	-8.579	6.063	1.00	70.93	A
853	N	ALA	109	30.259	-10.000	7.559	1.00	78.14	A
854	CA	ALA	109	30.902	-10.694	6.459	1.00	65.65	A
855	CB	ALA	109	31.922	-11.693	6.941	1.00	53.68	A
856	C	ALA	109	29.956	-11.276	5.449	1.00	79.51	A
857	O	ALA	109	30.250	-11.316	4.244	1.00	41.64	A
858	N	LYS	110	28.788	-11.641	5.926	1.00	39.90	A
859	CA	LYS	110	27.694	-12.164	5.096	1.00	48.96	A
860	CB	LYS	110	26.552	-12.675	6.025	1.00	59.00	A
861	CG	LYS	110	25.299	-13.301	5.421	1.00	93.24	A
862	CD	LYS	110	24.083	-13.343	6.416	1.00	109.99	A
863	CE	LYS	110	24.332	-14.284	7.623	1.00	125.36	A
864	NZ	LYS	110	23.626	-13.843	8.886	1.00	100.55	A
865	C	LYS	110	27.314	-10.884	4.324	1.00	78.46	A
866	O	LYS	110	27.715	-10.766	3.187	1.00	73.20	A
867	N	ASN	111	26.591	-9.933	4.921	1.00	71.12	A
868	CA	ASN	111	26.303	-8.676	4.240	1.00	63.14	A
869	CB	ASN	111	26.319	-7.479	5.227	1.00	33.14	A
870	CG	ASN	111	25.082	-7.412	6.117	1.00	82.69	A
871	OD1	ASN	111	24.145	-8.222	5.979	1.00	63.47	A
872	ND2	ASN	111	25.075	-6.424	7.064	1.00	44.74	A
873	C	ASN	111	27.400	-8.298	3.210	1.00	79.10	A
874	O	ASN	111	27.140	-7.836	2.094	1.00	65.98	A
875	N	LYS	112	28.656	-8.434	3.601	1.00	53.09	A
876	CA	LYS	112	29.684	-8.017	2.678	1.00	72.56	A
877	CB	LYS	112	31.076	-8.195	3.295	1.00	41.26	A
878	CG	LYS	112	32.229	-7.647	2.372	1.00	56.16	A
879	CD	LYS	112	33.670	-8.000	2.883	1.00	38.66	A
880	CE	LYS	112	34.609	-7.376	1.887	1.00	53.35	A
881	NZ	LYS	112	36.028	-7.667	2.257	1.00	55.96	A
882	C	LYS	112	29.598	-8.763	1.365	1.00	72.64	A
883	O	LYS	112	29.659	-8.199	.290	1.00	92.35	A
884	N	ILE	113	29.465	-10.064	1.490	1.00	90.12	A
885	CA	ILE	113	29.381	-11.007	.385	1.00	73.25	A
886	CB	ILE	113	29.432	-12.470	1.009	1.00	76.75	A
887	CG2	ILE	113	28.386	-13.349	.336	1.00	64.27	A
888	CG1	ILE	113	30.911	-13.016	1.015	1.00	48.95	A
889	CD1	ILE	113	32.042	-11.866	.878	1.00	79.86	A
890	C	ILE	113	28.107	-10.710	-.470	1.00	80.87	A
891	O	ILE	113	28.156	-10.715	-1.674	1.00	53.69	A
892	N	ALA	114	26.971	-10.448	.175	1.00	39.33	A
893	CA	ALA	114	25.766	-10.109	-.536	1.00	59.73	A
894	CB	ALA	114	24.623	-10.035	.451	1.00	41.55	A
895	C	ALA	114	25.853	-8.784	-1.380	1.00	75.68	A
896	O	ALA	114	25.074	-8.558	-2.301	1.00	100.52	A
897	N	LYS	115	26.820	-7.950	-1.044	1.00	66.26	A
898	CA	LYS	115	27.065	-6.674	-1.674	1.00	51.87	A
899	CB	LYS	115	27.702	-5.684	-.658	1.00	94.22	A
900	CG	LYS	115	28.373	-4.393	-1.232	1.00	71.45	A

901	CD	LYS	115	27.319	-3.474	-1.806	1.00	93.79	A
902	CE	LYS	115	27.777	-2.081	-2.207	1.00	80.61	A
903	NZ	LYS	115	26.503	-1.253	-2.088	1.00	64.02	A
904	C	LYS	115	28.012	-6.914	-2.816	1.00	50.60	A
905	O	LYS	115	27.946	-6.241	-3.862	1.00	83.35	A
906	N	GLU	116	28.958	-7.825	-2.626	1.00	50.27	A
907	CA	GLU	116	29.789	-8.109	-3.783	1.00	70.12	A
908	CB	GLU	116	31.028	-8.812	-3.376	1.00	51.12	A
909	CG	GLU	116	32.013	-8.874	-4.544	1.00	126.77	A
910	CD	GLU	116	33.094	-9.891	-4.334	1.00	143.83	A
911	OE1	GLU	116	33.211	-10.374	-3.179	1.00	123.58	A
912	OE2	GLU	116	33.813	-10.191	-5.324	1.00	126.19	A
913	C	GLU	116	29.002	-8.946	-4.875	1.00	76.29	A
914	O	GLU	116	29.412	-9.041	-6.004	1.00	64.68	A
915	N	THR	117	27.851	-9.502	-4.535	1.00	53.37	A
916	CA	THR	117	27.025	-10.237	-5.452	1.00	87.86	A
917	CB	THR	117	26.198	-11.249	-4.658	1.00	53.06	A
918	OG1	THR	117	26.971	-12.413	-4.574	1.00	61.44	A
919	CG2	THR	117	24.865	-11.567	-5.274	1.00	55.34	A
920	C	THR	117	26.170	-9.235	-6.205	1.00	99.90	A
921	O	THR	117	26.219	-9.196	-7.438	1.00	78.99	A
922	N	ASN	118	25.416	-8.417	-5.469	1.00	90.73	A
923	CA	ASN	118	24.574	-7.410	-6.115	1.00	83.59	A
924	CB	ASN	118	23.616	-6.763	-5.093	1.00	74.18	A
925	CG	ASN	118	22.731	-5.601	-5.673	1.00	100.94	A
926	OD1	ASN	118	23.230	-4.617	-6.225	1.00	96.09	A
927	ND2	ASN	118	21.413	-5.708	-5.476	1.00	79.75	A
928	C	ASN	118	25.464	-6.384	-6.829	1.00	64.79	A
929	O	ASN	118	24.979	-5.402	-7.390	1.00	100.88	A
930	N	ASN	119	26.767	-6.635	-6.854	1.00	68.47	A
931	CA	ASN	119	27.714	-5.757	-7.539	1.00	70.67	A
932	CB	ASN	119	28.874	-5.468	-6.578	1.00	101.08	A
933	CG	ASN	119	28.947	-3.981	-6.130	1.00	81.52	A
934	OD1	ASN	119	30.010	-3.444	-6.194	1.00	76.29	A
935	ND2	ASN	119	27.810	-3.329	-5.684	1.00	52.81	A
936	C	ASN	119	28.257	-6.436	-8.794	1.00	74.91	A
937	O	ASN	119	28.659	-5.814	-9.772	1.00	89.97	A
938	N	LYS	120	28.323	-7.756	-8.720	1.00	101.14	A
939	CA	LYS	120	28.814	-8.533	-9.823	1.00	63.13	A
940	CB	LYS	120	29.185	-9.945	-9.370	1.00	75.36	A
941	CG	LYS	120	30.668	-9.993	-9.402	1.00	79.68	A
942	CD	LYS	120	31.302	-11.118	-8.726	1.00	62.55	A
943	CE	LYS	120	32.851	-10.892	-8.922	1.00	71.66	A
944	NZ	LYS	120	33.568	-12.237	-8.830	1.00	89.23	A
945	C	LYS	120	27.646	-8.533	-10.776	1.00	98.18	A
946	O	LYS	120	27.793	-8.504	-11.999	1.00	52.62	A
947	N	LYS	121	26.459	-8.561	-10.181	1.00	37.74	A
948	CA	LYS	121	25.298	-8.470	-10.992	1.00	52.49	A
949	CB	LYS	121	24.104	-8.444	-10.122	1.00	26.27	A
950	CG	LYS	121	22.747	-8.315	-10.832	1.00	58.52	A
951	CD	LYS	121	21.623	-8.305	-9.711	1.00	41.56	A

952	CE	LYS	121	20.187	-8.411	-10.327	1.00	87.58	A
953	NZ	LYS	121	19.061	-8.356	-9.284	1.00	75.03	A
954	C	LYS	121	25.273	-7.162	-11.826	1.00	92.55	A
955	O	LYS	121	25.151	-7.148	-13.070	1.00	77.63	A
956	N	LYS	122	25.289	-6.063	-11.089	1.00	86.42	A
957	CA	LYS	122	25.236	-4.747	-11.683	1.00	67.80	A
958	CB	LYS	122	25.359	-3.663	-10.596	1.00	87.76	A
959	CG	LYS	122	24.017	-3.227	-10.027	1.00	93.79	A
960	CD	LYS	122	24.204	-2.005	-9.161	1.00	94.99	A
961	CE	LYS	122	22.934	-1.638	-8.401	1.00	96.67	A
962	NZ	LYS	122	23.288	-.584	-7.394	1.00	104.41	A
963	C	LYS	122	26.315	-4.572	-12.728	1.00	57.05	A
964	O	LYS	122	26.151	-3.784	-13.670	1.00	92.39	A
965	N	GLU	123	27.377	-5.349	-12.630	1.00	62.16	A
966	CA	GLU	123	28.486	-5.216	-13.632	1.00	74.30	A
967	CB	GLU	123	29.803	-5.587	-12.927	1.00	93.87	A
968	CG	GLU	123	31.079	-5.662	-13.734	1.00	102.46	A
969	CD	GLU	123	32.076	-6.655	-13.084	1.00	121.86	A
970	OE1	GLU	123	31.770	-7.128	-11.962	1.00	131.14	A
971	OE2	GLU	123	33.148	-6.978	-13.666	1.00	101.22	A
972	C	GLU	123	28.249	-6.118	-14.869	1.00	90.60	A
973	O	GLU	123	28.863	-5.947	-15.926	1.00	86.68	A
974	N	PHE	124	27.323	-7.059	-14.714	1.00	80.58	A
975	CA	PHE	124	26.945	-8.068	-15.705	1.00	73.98	A
976	CB	PHE	124	26.289	-9.240	-14.957	1.00	96.58	A
977	CG	PHE	124	25.602	-10.230	-15.835	1.00	77.75	A
978	CD1	PHE	124	26.345	-11.066	-16.652	1.00	105.70	A
979	CD2	PHE	124	24.201	-10.285	-15.889	1.00	95.12	A
980	CE1	PHE	124	25.709	-11.945	-17.514	1.00	75.75	A
981	CE2	PHE	124	23.544	-11.157	-16.758	1.00	66.78	A
982	CZ	PHE	124	24.300	-11.985	-17.566	1.00	92.76	A
983	C	PHE	124	25.961	-7.379	-16.633	1.00	79.93	A
984	O	PHE	124	26.165	-7.372	-17.843	1.00	54.05	A
985	N	GLU	125	24.870	-6.896	-16.035	1.00	43.78	A
986	CA	GLU	125	23.855	-6.064	-16.689	1.00	69.62	A
987	CB	GLU	125	22.930	-5.411	-15.655	1.00	42.14	A
988	CG	GLU	125	22.141	-6.478	-14.991	1.00	58.93	A
989	CD	GLU	125	21.102	-5.960	-14.035	1.00	88.06	A
990	OE1	GLU	125	21.372	-4.906	-13.446	1.00	86.83	A
991	OE2	GLU	125	20.038	-6.624	-13.864	1.00	91.30	A
992	C	GLU	125	24.516	-4.919	-17.478	1.00	79.50	A
993	O	GLU	125	24.198	-4.633	-18.633	1.00	84.76	A
994	N	GLU	126	25.417	-4.228	-16.835	1.00	71.96	A
995	CA	GLU	126	26.088	-3.203	-17.561	1.00	87.34	A
996	CB	GLU	126	27.202	-2.619	-16.690	1.00	103.77	A
997	CG	GLU	126	28.154	-1.693	-17.413	1.00	132.71	A
998	CD	GLU	126	29.611	-1.969	-17.042	1.00	152.62	A
999	OE1	GLU	126	30.167	-3.021	-17.471	1.00	147.53	A
1000	OE2	GLU	126	30.189	-1.132	-16.310	1.00	157.10	A
1001	C	GLU	126	26.653	-3.794	-18.873	1.00	55.58	A
1002	O	GLU	126	26.373	-3.286	-19.953	1.00	79.91	A

1003	N	THR	127	27.481	-4.830	-18.785	1.00	64.23	A
1004	CA	THR	127	28.114	-5.453	-19.966	1.00	67.14	A
1005	CB	THR	127	29.065	-6.524	-19.454	1.00	66.95	A
1006	OG1	THR	127	30.395	-6.033	-19.606	1.00	73.01	A
1007	CG2	THR	127	28.891	-7.843	-20.181	1.00	102.50	A
1008	C	THR	127	27.126	-6.018	-21.048	1.00	78.77	A
1009	O	THR	127	27.432	-6.080	-22.206	1.00	65.23	A
1010	N	ALA	128	25.954	-6.445	-20.634	1.00	50.29	A
1011	CA	ALA	128	24.934	-6.929	-21.480	1.00	55.01	A
1012	CB	ALA	128	23.800	-7.425	-20.622	1.00	51.04	A
1013	C	ALA	128	24.480	-5.724	-22.325	1.00	90.73	A
1014	O	ALA	128	24.531	-5.780	-23.564	1.00	55.11	A
1015	N	LYS	129	24.062	-4.641	-21.653	1.00	73.40	A
1016	CA	LYS	129	23.613	-3.414	-22.338	1.00	65.13	A
1017	CB	LYS	129	23.493	-2.216	-21.357	1.00	64.28	A
1018	CG	LYS	129	22.090	-1.930	-20.851	1.00	89.21	A
1019	CD	LYS	129	21.668	-.456	-21.000	1.00	86.65	A
1020	CE	LYS	129	20.140	-.238	-20.675	1.00	89.28	A
1021	NZ	LYS	129	19.624	1.180	-20.861	1.00	101.21	A
1022	C	LYS	129	24.566	-3.017	-23.488	1.00	58.30	A
1023	O	LYS	129	24.142	-2.599	-24.568	1.00	81.13	A
1024	N	LYS	130	25.859	-3.200	-23.273	1.00	53.11	A
1025	CA	LYS	130	26.814	-2.834	-24.295	1.00	68.18	A
1026	CB	LYS	130	28.191	-2.602	-23.676	1.00	65.51	A
1027	CG	LYS	130	28.179	-1.652	-22.464	1.00	92.18	A
1028	CD	LYS	130	29.631	-1.469	-21.984	1.00	112.54	A
1029	CE	LYS	130	29.771	-.331	-20.959	1.00	137.84	A
1030	NZ	LYS	130	31.174	-.167	-20.438	1.00	145.29	A
1031	C	LYS	130	26.904	-3.907	-25.348	1.00	77.89	A
1032	O	LYS	130	27.329	-3.646	-26.451	1.00	87.80	A
1033	N	VAL	131	26.501	-5.127	-25.024	1.00	71.61	A
1034	CA	VAL	131	26.642	-6.148	-26.018	1.00	56.82	A
1035	CB	VAL	131	26.774	-7.554	-25.357	1.00	76.33	A
1036	CG1	VAL	131	25.472	-8.393	-25.418	1.00	55.25	A
1037	CG2	VAL	131	27.859	-8.253	-26.027	1.00	53.30	A
1038	C	VAL	131	25.408	-5.956	-26.865	1.00	80.61	A
1039	O	VAL	131	25.513	-5.894	-28.070	1.00	53.49	A
1040	N	ARG	132	24.245	-5.827	-26.223	1.00	44.94	A
1041	CA	ARG	132	23.033	-5.572	-26.932	1.00	58.99	A
1042	CB	ARG	132	21.923	-5.234	-25.947	1.00	46.50	A
1043	CG	ARG	132	20.801	-4.417	-26.635	1.00	71.89	A
1044	CD	ARG	132	19.528	-4.454	-25.805	1.00	87.26	A
1045	NE	ARG	132	18.435	-3.769	-26.519	1.00	110.12	A
1046	CZ	ARG	132	17.184	-3.610	-26.065	1.00	130.03	A
1047	NH1	ARG	132	16.828	-4.100	-24.860	1.00	114.25	A
1048	NH2	ARG	132	16.288	-2.939	-26.821	1.00	75.58	A
1049	C	ARG	132	23.172	-4.401	-27.966	1.00	89.29	A
1050	O	ARG	132	22.968	-4.541	-29.204	1.00	65.79	A
1051	N	ARG	133	23.522	-3.246	-27.419	1.00	76.62	A
1052	CA	ARG	133	23.672	-2.051	-28.221	1.00	75.34	A
1053	CB	ARG	133	24.276	-.920	-27.334	1.00	105.86	A

1054	CG	ARG	133	24.109	.538	-27.851	1.00	143.42	A
1055	CD	ARG	133	24.834	1.568	-26.927	1.00	153.27	A
1056	NE	ARG	133	24.901	2.947	-27.458	1.00	167.80	A
1057	CZ	ARG	133	25.821	3.867	-27.115	1.00	160.91	A
1058	NH1	ARG	133	26.775	3.578	-26.232	1.00	144.63	A
1059	NH2	ARG	133	25.805	5.085	-27.661	1.00	156.92	A
1060	C	ARG	133	24.543	-2.322	-29.455	1.00	53.07	A
1061	O	ARG	133	24.208	-1.981	-30.606	1.00	101.92	A
1062	N	ALA	134	25.663	-2.951	-29.211	1.00	51.44	A
1063	CA	ALA	134	26.615	-3.220	-30.259	1.00	53.16	A
1064	CB	ALA	134	27.819	-3.880	-29.682	1.00	53.00	A
1065	C	ALA	134	26.044	-4.109	-31.346	1.00	88.15	A
1066	O	ALA	134	26.441	-3.969	-32.479	1.00	74.98	A
1067	N	ILE	135	25.129	-5.017	-31.000	1.00	62.61	A
1068	CA	ILE	135	24.536	-5.946	-31.954	1.00	75.16	A
1069	CB	ILE	135	23.767	-7.047	-31.183	1.00	87.33	A
1070	CG2	ILE	135	22.698	-7.519	-32.039	1.00	75.59	A
1071	CG1	ILE	135	24.687	-8.187	-30.688	1.00	71.52	A
1072	CD1	ILE	135	26.027	-7.680	-30.130	1.00	85.99	A
1073	C	ILE	135	23.574	-5.189	-32.910	1.00	85.48	A
1074	O	ILE	135	23.590	-5.361	-34.141	1.00	67.79	A
1075	N	GLU	136	22.716	-4.385	-32.303	1.00	63.09	A
1076	CA	GLU	136	21.774	-3.521	-32.993	1.00	65.85	A
1077	CB	GLU	136	21.056	-2.649	-31.980	1.00	71.62	A
1078	CG	GLU	136	20.182	-3.447	-30.945	1.00	64.89	A
1079	CD	GLU	136	19.518	-2.543	-29.860	1.00	111.14	A
1080	OE1	GLU	136	20.168	-1.477	-29.550	1.00	91.79	A
1081	OE2	GLU	136	18.384	-2.918	-29.335	1.00	72.46	A
1082	C	GLU	136	22.499	-2.618	-34.016	1.00	63.36	A
1083	O	GLU	136	21.990	-2.372	-35.103	1.00	100.43	A
1084	N	GLN	137	23.687	-2.147	-33.693	1.00	70.95	A
1085	CA	GLN	137	24.416	-1.301	-34.623	1.00	73.25	A
1086	CB	GLN	137	25.556	-.575	-33.890	1.00	88.07	A
1087	CG	GLN	137	25.057	.701	-33.193	1.00	116.32	A
1088	CD	GLN	137	26.142	1.426	-32.426	1.00	123.67	A
1089	OE1	GLN	137	27.272	1.575	-32.916	1.00	98.34	A
1090	NE2	GLN	137	25.807	1.895	-31.224	1.00	114.41	A
1091	C	GLN	137	24.961	-2.129	-35.761	1.00	84.58	A
1092	O	GLN	137	25.429	-1.649	-36.778	1.00	101.16	A
1093	N	LEU	138	24.888	-3.413	-35.594	1.00	91.34	A
1094	CA	LEU	138	25.401	-4.280	-36.611	1.00	81.46	A
1095	CB	LEU	138	26.399	-5.221	-35.952	1.00	65.30	A
1096	CG	LEU	138	27.889	-5.227	-36.258	1.00	74.08	A
1097	CD1	LEU	138	28.483	-3.848	-36.311	1.00	78.33	A
1098	CD2	LEU	138	28.539	-6.076	-35.195	1.00	72.79	A
1099	C	LEU	138	24.183	-5.054	-37.142	1.00	98.62	A
1100	O	LEU	138	24.200	-6.279	-37.365	1.00	95.49	A
1101	N	ALA	139	23.121	-4.308	-37.343	1.00	94.08	A
1102	CA	ALA	139	21.898	-4.888	-37.805	1.00	90.55	A
1103	CB	ALA	139	21.197	-5.574	-36.626	1.00	68.35	A
1104	C	ALA	139	21.130	-3.667	-38.293	1.00	112.47	A

1105	O	ALA	139	19.985	-3.414	-37.897	1.00	111.79	A
1106	N	ALA	140	21.798	-2.886	-39.133	1.00	100.83	A
1107	CA	ALA	140	21.211	-1.676	-39.680	1.00	107.51	A
1108	CB	ALA	140	20.963	-.643	-38.548	1.00	75.32	A
1109	C	ALA	140	22.230	-1.147	-40.664	1.00	118.66	A
1110	O	ALA	140	23.354	-1.712	-40.671	1.00	90.11	A
1111	OXT	ALA	140	21.898	-.180	-41.390	1.00	134.12	A
1112	CB	LEU	6	38.688	-16.023	16.490	1.00	95.85	B
1113	CG	LEU	6	39.282	-15.873	17.908	1.00	105.59	B
1114	CD1	LEU	6	40.777	-15.439	17.922	1.00	67.52	B
1115	CD2	LEU	6	38.496	-14.824	18.615	1.00	99.04	B
1116	C	LEU	6	40.616	-15.087	15.120	1.00	108.25	B
1117	O	LEU	6	41.075	-16.193	14.809	1.00	96.42	B
1118	N	LEU	6	38.190	-15.030	14.292	1.00	96.14	B
1119	CA	LEU	6	39.098	-14.944	15.480	1.00	107.62	B
1120	N	PRO	7	41.411	-13.982	15.217	1.00	112.84	B
1121	CD	PRO	7	41.002	-12.676	15.771	1.00	78.65	B
1122	CA	PRO	7	42.854	-13.933	14.909	1.00	86.27	B
1123	CB	PRO	7	43.301	-12.596	15.483	1.00	62.96	B
1124	CG	PRO	7	42.260	-12.245	16.425	1.00	96.69	B
1125	C	PRO	7	43.697	-15.066	15.389	1.00	87.03	B
1126	O	PRO	7	43.168	-16.011	15.932	1.00	113.44	B
1127	N	PRO	8	45.029	-14.983	15.199	1.00	92.14	B
1128	CD	PRO	8	45.716	-13.979	14.368	1.00	115.96	B
1129	CA	PRO	8	45.985	-16.024	15.621	1.00	123.92	B
1130	CB	PRO	8	46.877	-16.158	14.401	1.00	127.96	B
1131	CG	PRO	8	47.088	-14.678	14.061	1.00	140.92	B
1132	C	PRO	8	46.832	-15.721	16.878	1.00	127.59	B
1133	O	PRO	8	47.895	-16.340	17.087	1.00	116.93	B
1134	N	ALA	9	46.396	-14.768	17.696	1.00	121.29	B
1135	CA	ALA	9	47.155	-14.442	18.892	1.00	98.67	B
1136	CB	ALA	9	47.666	-13.051	18.807	1.00	81.03	B
1137	C	ALA	9	46.220	-14.593	20.063	1.00	79.23	B
1138	O	ALA	9	46.651	-14.721	21.198	1.00	105.21	B
1139	N	TRP	10	44.937	-14.611	19.743	1.00	70.53	B
1140	CA	TRP	10	43.879	-14.745	20.713	1.00	70.37	B
1141	CB	TRP	10	42.667	-13.882	20.294	1.00	85.23	B
1142	CG	TRP	10	42.847	-12.382	20.221	1.00	121.47	B
1143	CD2	TRP	10	41.779	-11.418	20.154	1.00	127.74	B
1144	CE2	TRP	10	42.375	-10.135	20.029	1.00	139.10	B
1145	CE3	TRP	10	40.354	-11.520	20.165	1.00	109.61	B
1146	CD1	TRP	10	44.028	-11.663	20.151	1.00	121.21	B
1147	NE1	TRP	10	43.744	-10.315	20.037	1.00	134.47	B
1148	CZ2	TRP	10	41.598	-8.949	19.938	1.00	139.88	B
1149	CZ3	TRP	10	39.567	-10.335	20.072	1.00	86.13	B
1150	CH2	TRP	10	40.203	-9.074	19.952	1.00	137.74	B
1151	C	TRP	10	43.416	-16.196	20.779	1.00	85.56	B
1152	O	TRP	10	42.505	-16.557	21.576	1.00	59.83	B
1153	N	GLN	11	44.011	-17.036	19.940	1.00	77.82	B
1154	CA	GLN	11	43.517	-18.392	19.906	1.00	75.51	B
1155	CB	GLN	11	44.157	-19.151	18.801	1.00	69.11	B

1156	CG	GLN	11	43.584	-18.727	17.525	1.00	91.39	B
1157	CD	GLN	11	44.205	-19.450	16.389	1.00	102.63	B
1158	OE1	GLN	11	45.401	-19.310	16.137	1.00	91.08	B
1159	NE2	GLN	11	43.407	-20.252	15.696	1.00	113.26	B
1160	C	GLN	11	43.694	-19.125	21.204	1.00	84.73	B
1161	O	GLN	11	42.762	-19.814	21.620	1.00	50.95	B
1162	N	PRO	12	44.866	-18.970	21.878	1.00	42.57	B
1163	CD	PRO	12	46.017	-18.284	21.243	1.00	66.76	B
1164	CA	PRO	12	45.279	-19.566	23.162	1.00	41.80	B
1165	CB	PRO	12	46.502	-18.763	23.501	1.00	78.28	B
1166	CG	PRO	12	47.162	-18.644	22.163	1.00	46.33	B
1167	C	PRO	12	44.157	-19.472	24.194	1.00	55.59	B
1168	O	PRO	12	43.903	-20.370	25.062	1.00	62.45	B
1169	N	PHE	13	43.401	-18.421	23.945	1.00	38.61	B
1170	CA	PHE	13	42.308	-17.965	24.775	1.00	45.65	B
1171	CB	PHE	13	41.944	-16.455	24.451	1.00	59.69	B
1172	CG	PHE	13	42.563	-15.445	25.372	1.00	48.62	B
1173	CD1	PHE	13	43.756	-14.862	25.040	1.00	52.98	B
1174	CD2	PHE	13	42.004	-15.140	26.636	1.00	65.40	B
1175	CE1	PHE	13	44.419	-13.975	25.956	1.00	56.37	B
1176	CE2	PHE	13	42.673	-14.253	27.587	1.00	49.21	B
1177	CZ	PHE	13	43.865	-13.686	27.229	1.00	68.97	B
1178	C	PHE	13	41.122	-18.879	24.632	1.00	48.97	B
1179	O	PHE	13	40.115	-18.860	25.458	1.00	58.00	B
1180	N	LEU	14	41.265	-19.722	23.644	1.00	48.79	B
1181	CA	LEU	14	40.206	-20.673	23.298	1.00	75.24	B
1182	CB	LEU	14	40.051	-20.633	21.790	1.00	78.19	B
1183	CG	LEU	14	39.122	-19.506	21.432	1.00	95.80	B
1184	CD1	LEU	14	39.121	-19.301	19.870	1.00	74.33	B
1185	CD2	LEU	14	37.707	-19.886	22.063	1.00	67.39	B
1186	C	LEU	14	40.508	-22.125	23.704	1.00	45.57	B
1187	O	LEU	14	41.574	-22.656	23.258	1.00	49.13	B
1188	N	LYS	15	39.628	-22.776	24.491	1.00	50.09	B
1189	CA	LYS	15	39.913	-24.178	24.867	1.00	70.66	B
1190	CB	LYS	15	38.742	-24.800	25.576	1.00	65.82	B
1191	CG	LYS	15	39.220	-25.954	26.522	1.00	57.44	B
1192	CD	LYS	15	38.000	-26.447	27.315	1.00	67.07	B
1193	CE	LYS	15	38.192	-27.914	27.807	1.00	81.71	B
1194	NZ	LYS	15	37.039	-28.483	28.634	1.00	88.85	B
1195	C	LYS	15	40.318	-25.065	23.689	1.00	62.30	B
1196	O	LYS	15	41.448	-25.622	23.655	1.00	68.00	B
1197	N	ASP	16	39.408	-25.180	22.717	1.00	80.85	B
1198	CA	ASP	16	39.670	-25.969	21.503	1.00	75.48	B
1199	CB	ASP	16	38.624	-25.664	20.429	1.00	84.79	B
1200	CG	ASP	16	37.227	-26.215	20.803	1.00	100.35	B
1201	OD1	ASP	16	36.577	-25.655	21.696	1.00	129.22	B
1202	OD2	ASP	16	36.767	-27.214	20.230	1.00	110.54	B
1203	C	ASP	16	41.075	-25.778	20.931	1.00	65.77	B
1204	O	ASP	16	41.781	-26.756	20.618	1.00	77.38	B
1205	N	HIS	17	41.525	-24.534	20.821	1.00	71.68	B
1206	CA	HIS	17	42.856	-24.360	20.264	1.00	80.83	B

1207	CB	HIS	17	43.110	-22.878	19.811	1.00	41.66	B
1208	CG	HIS	17	44.561	-22.600	19.478	1.00	33.44	B
1209	CD2	HIS	17	45.578	-22.130	20.266	1.00	81.18	B
1210	ND1	HIS	17	45.149	-22.961	18.281	1.00	78.79	B
1211	CE1	HIS	17	46.459	-22.727	18.337	1.00	55.52	B
1212	NE2	HIS	17	46.743	-22.225	19.532	1.00	63.79	B
1213	C	HIS	17	43.913	-24.846	21.260	1.00	58.60	B
1214	O	HIS	17	45.044	-25.263	20.873	1.00	59.22	B
1215	N	ARG	18	43.593	-24.769	22.546	1.00	72.91	B
1216	CA	ARG	18	44.598	-25.202	23.490	1.00	59.67	B
1217	CB	ARG	18	44.203	-24.772	24.854	1.00	89.68	B
1218	CG	ARG	18	45.030	-23.610	25.363	1.00	54.47	B
1219	CD	ARG	18	44.296	-23.305	26.712	1.00	49.52	B
1220	NE	ARG	18	43.206	-22.379	26.473	1.00	46.44	B
1221	CZ	ARG	18	42.073	-22.360	27.150	1.00	71.37	B
1222	NH1	ARG	18	41.844	-23.242	28.098	1.00	64.71	B
1223	NH2	ARG	18	41.200	-21.367	26.970	1.00	48.93	B
1224	C	ARG	18	44.671	-26.731	23.307	1.00	85.74	B
1225	O	ARG	18	45.768	-27.319	23.198	1.00	40.57	B
1226	N	ILE	19	43.531	-27.395	23.182	1.00	49.23	B
1227	CA	ILE	19	43.605	-28.847	22.967	1.00	67.05	B
1228	CB	ILE	19	42.235	-29.505	22.850	1.00	58.61	B
1229	CG2	ILE	19	42.410	-30.843	22.328	1.00	65.21	B
1230	CG1	ILE	19	41.516	-29.543	24.188	1.00	61.82	B
1231	CD1	ILE	19	40.122	-29.861	24.040	1.00	62.05	B
1232	C	ILE	19	44.312	-29.157	21.647	1.00	66.58	B
1233	O	ILE	19	45.141	-30.051	21.558	1.00	82.50	B
1234	N	SER	20	43.932	-28.438	20.603	1.00	78.00	B
1235	CA	SER	20	44.546	-28.658	19.321	1.00	58.83	B
1236	CB	SER	20	44.210	-27.462	18.359	1.00	78.21	B
1237	OG	SER	20	45.352	-26.732	17.774	1.00	66.58	B
1238	C	SER	20	46.052	-28.804	19.531	1.00	61.94	B
1239	O	SER	20	46.692	-29.483	18.758	1.00	81.95	B
1240	N	THR	21	46.641	-28.196	20.561	1.00	70.55	B
1241	CA	THR	21	48.103	-28.284	20.687	1.00	79.30	B
1242	CB	THR	21	48.685	-27.174	21.563	1.00	97.72	B
1243	OG1	THR	21	48.087	-27.227	22.880	1.00	54.94	B
1244	CG2	THR	21	48.454	-25.848	20.913	1.00	86.41	B
1245	C	THR	21	48.710	-29.561	21.216	1.00	83.74	B
1246	O	THR	21	49.921	-29.743	21.088	1.00	66.96	B
1247	N	PHE	22	47.921	-30.436	21.843	1.00	94.22	B
1248	CA	PHE	22	48.481	-31.698	22.363	1.00	100.81	B
1249	CB	PHE	22	47.647	-32.199	23.538	1.00	77.94	B
1250	CG	PHE	22	47.631	-31.218	24.672	1.00	97.07	B
1251	CD1	PHE	22	46.474	-30.522	25.027	1.00	73.82	B
1252	CD2	PHE	22	48.812	-30.882	25.303	1.00	92.51	B
1253	CE1	PHE	22	46.516	-29.516	25.983	1.00	104.62	B
1254	CE2	PHE	22	48.852	-29.852	26.279	1.00	92.29	B
1255	CZ	PHE	22	47.721	-29.186	26.607	1.00	101.70	B
1256	C	PHE	22	48.604	-32.728	21.246	1.00	101.28	B
1257	O	PHE	22	47.618	-33.350	20.814	1.00	78.23	B

1258	N	LYS	23	49.852	-32.799	20.760	1.00	87.05	B
1259	CA	LYS	23	50.355	-33.665	19.681	1.00	115.78	B
1260	CB	LYS	23	51.778	-33.197	19.257	1.00	122.91	B
1261	CG	LYS	23	52.320	-33.841	17.960	1.00	144.39	B
1262	CD	LYS	23	52.533	-32.810	16.841	1.00	156.59	B
1263	CE	LYS	23	52.711	-33.464	15.444	1.00	147.39	B
1264	NZ	LYS	23	52.906	-32.441	14.358	1.00	146.41	B
1265	C	LYS	23	50.401	-35.114	20.187	1.00	124.49	B
1266	O	LYS	23	49.441	-35.893	19.995	1.00	107.06	B
1267	N	ASN	24	51.514	-35.496	20.805	1.00	89.06	B
1268	CA	ASN	24	51.546	-36.823	21.359	1.00	89.80	B
1269	CB	ASN	24	52.972	-37.233	21.688	1.00	94.26	B
1270	CG	ASN	24	53.203	-38.733	21.533	1.00	139.50	B
1271	OD1	ASN	24	54.273	-39.246	21.845	1.00	131.13	B
1272	ND2	ASN	24	52.200	-39.437	21.041	1.00	153.04	B
1273	C	ASN	24	50.705	-36.759	22.657	1.00	94.10	B
1274	O	ASN	24	49.480	-36.880	22.663	1.00	122.66	B
1275	N	TRP	25	51.377	-36.520	23.756	1.00	103.93	B
1276	CA	TRP	25	50.757	-36.453	25.066	1.00	128.61	B
1277	CB	TRP	25	49.457	-35.618	25.140	1.00	104.24	B
1278	CG	TRP	25	49.276	-35.117	26.582	1.00	64.27	B
1279	CD2	TRP	25	50.201	-34.313	27.358	1.00	95.38	B
1280	CE2	TRP	25	49.755	-34.286	28.695	1.00	89.71	B
1281	CE3	TRP	25	51.395	-33.645	27.035	1.00	103.44	B
1282	CD1	TRP	25	48.313	-35.499	27.470	1.00	61.90	B
1283	NE1	TRP	25	48.590	-35.016	28.748	1.00	84.91	B
1284	CZ2	TRP	25	50.439	-33.587	29.716	1.00	57.48	B
1285	CZ3	TRP	25	52.073	-32.964	28.049	1.00	98.22	B
1286	CH2	TRP	25	51.604	-32.949	29.374	1.00	63.72	B
1287	C	TRP	25	50.514	-37.875	25.462	1.00	132.91	B
1288	O	TRP	25	49.448	-38.453	25.244	1.00	129.53	B
1289	N	PRO	26	51.546	-38.469	26.045	1.00	119.75	B
1290	CD	PRO	26	52.873	-37.859	26.288	1.00	114.50	B
1291	CA	PRO	26	51.504	-39.841	26.492	1.00	107.25	B
1292	CB	PRO	26	52.833	-39.972	27.238	1.00	126.13	B
1293	CG	PRO	26	53.770	-39.047	26.442	1.00	124.99	B
1294	C	PRO	26	50.297	-40.186	27.367	1.00	119.56	B
1295	O	PRO	26	50.193	-41.319	27.825	1.00	155.74	B
1296	N	PHE	27	49.372	-39.255	27.589	1.00	96.35	B
1297	CA	PHE	27	48.250	-39.544	28.495	1.00	99.21	B
1298	CB	PHE	27	48.421	-38.725	29.772	1.00	80.36	B
1299	CG	PHE	27	49.812	-38.749	30.306	1.00	94.49	B
1300	CD1	PHE	27	50.811	-38.004	29.679	1.00	96.54	B
1301	CD2	PHE	27	50.161	-39.614	31.346	1.00	96.49	B
1302	CE1	PHE	27	52.128	-38.126	30.070	1.00	113.34	B
1303	CE2	PHE	27	51.479	-39.748	31.750	1.00	99.38	B
1304	CZ	PHE	27	52.464	-39.004	31.109	1.00	120.24	B
1305	C	PHE	27	46.867	-39.315	27.937	1.00	101.14	B
1306	O	PHE	27	46.492	-38.183	27.665	1.00	121.68	B
1307	N	LEU	28	46.081	-40.382	27.803	1.00	90.49	B
1308	CA	LEU	28	44.756	-40.238	27.222	1.00	69.88	B

1309	CB	LEU	28	44.771	-40.797	25.779	1.00	98.65	B
1310	CG	LEU	28	45.895	-40.157	24.916	1.00	113.96	B
1311	CD1	LEU	28	46.159	-40.893	23.613	1.00	82.24	B
1312	CD2	LEU	28	45.539	-38.732	24.638	1.00	99.27	B
1313	C	LEU	28	43.622	-40.812	28.040	1.00	65.29	B
1314	O	LEU	28	43.571	-40.615	29.256	1.00	115.01	B
1315	N	GLU	29	42.701	-41.496	27.369	1.00	86.27	B
1316	CA	GLU	29	41.552	-42.129	28.025	1.00	106.40	B
1317	CB	GLU	29	40.767	-43.015	27.031	1.00	127.09	B
1318	CG	GLU	29	41.187	-42.875	25.546	1.00	148.41	B
1319	CD	GLU	29	42.133	-43.996	25.073	1.00	167.83	B
1320	OE1	GLU	29	41.731	-45.183	25.097	1.00	165.39	B
1321	OE2	GLU	29	43.282	-43.698	24.675	1.00	152.29	B
1322	C	GLU	29	42.126	-42.970	29.165	1.00	102.05	B
1323	O	GLU	29	43.123	-43.695	29.009	1.00	78.00	B
1324	N	GLY	30	41.509	-42.865	30.323	1.00	86.08	B
1325	CA	GLY	30	42.044	-43.575	31.450	1.00	64.74	B
1326	C	GLY	30	42.725	-42.611	32.407	1.00	95.67	B
1327	O	GLY	30	42.544	-42.673	33.619	1.00	85.95	B
1328	N	CYS	31	43.514	-41.697	31.866	1.00	86.21	B
1329	CA	CYS	31	44.206	-40.744	32.705	1.00	97.49	B
1330	CB	CYS	31	45.354	-40.197	31.914	1.00	98.50	B
1331	SG	CYS	31	46.469	-41.487	31.375	1.00	94.78	B
1332	C	CYS	31	43.325	-39.586	33.193	1.00	111.06	B
1333	O	CYS	31	42.217	-39.410	32.685	1.00	108.68	B
1334	N	ALA	32	43.806	-38.800	34.168	1.00	95.11	B
1335	CA	ALA	32	43.039	-37.636	34.668	1.00	96.63	B
1336	CB	ALA	32	43.067	-37.559	36.241	1.00	66.49	B
1337	C	ALA	32	43.631	-36.337	34.065	1.00	81.07	B
1338	O	ALA	32	42.986	-35.274	34.043	1.00	76.90	B
1339	N	CYS	33	44.841	-36.502	33.537	1.00	69.70	B
1340	CA	CYS	33	45.718	-35.500	32.924	1.00	54.86	B
1341	CB	CYS	33	47.184	-35.904	33.269	1.00	63.86	B
1342	SG	CYS	33	48.386	-34.677	33.066	1.00	105.43	B
1343	C	CYS	33	45.545	-35.539	31.420	1.00	66.91	B
1344	O	CYS	33	46.552	-35.492	30.667	1.00	55.73	B
1345	N	THR	34	44.292	-35.655	30.977	1.00	81.40	B
1346	CA	THR	34	43.970	-35.714	29.544	1.00	89.31	B
1347	CB	THR	34	42.548	-36.171	29.271	1.00	84.47	B
1348	OG1	THR	34	41.647	-35.334	29.985	1.00	74.56	B
1349	CG2	THR	34	42.353	-37.596	29.696	1.00	96.13	B
1350	C	THR	34	44.120	-34.383	28.842	1.00	97.02	B
1351	O	THR	34	44.148	-33.317	29.470	1.00	113.24	B
1352	N	PRO	35	44.211	-34.427	27.511	1.00	92.86	B
1353	CD	PRO	35	44.459	-35.559	26.615	1.00	114.13	B
1354	CA	PRO	35	44.366	-33.176	26.787	1.00	103.11	B
1355	CB	PRO	35	44.508	-33.650	25.347	1.00	105.80	B
1356	CG	PRO	35	45.283	-34.893	25.529	1.00	87.32	B
1357	C	PRO	35	43.214	-32.209	27.046	1.00	92.56	B
1358	O	PRO	35	43.424	-30.995	27.117	1.00	99.70	B
1359	N	GLU	36	42.006	-32.734	27.229	1.00	69.06	B

1360	CA	GLU	36	40.924	-31.837	27.520	1.00	74.16	B
1361	CB	GLU	36	39.549	-32.520	27.523	1.00	53.77	B
1362	CG	GLU	36	38.482	-31.463	27.795	1.00	108.53	B
1363	CD	GLU	36	37.232	-31.974	28.481	1.00	130.99	B
1364	OE1	GLU	36	36.506	-32.776	27.843	1.00	124.88	B
1365	OE2	GLU	36	36.976	-31.555	29.645	1.00	134.28	B
1366	C	GLU	36	41.093	-31.156	28.865	1.00	89.28	B
1367	O	GLU	36	40.954	-29.940	28.940	1.00	107.85	B
1368	N	ARG	37	41.366	-31.922	29.926	1.00	110.97	B
1369	CA	ARG	37	41.506	-31.348	31.285	1.00	92.49	B
1370	CB	ARG	37	41.501	-32.450	32.379	1.00	66.82	B
1371	CG	ARG	37	40.102	-32.713	33.080	1.00	69.24	B
1372	CD	ARG	37	40.117	-34.130	33.651	1.00	126.98	B
1373	NE	ARG	37	38.866	-34.579	34.258	1.00	156.28	B
1374	CZ	ARG	37	38.611	-35.853	34.570	1.00	158.37	B
1375	NH1	ARG	37	39.512	-36.797	34.315	1.00	144.18	B
1376	NH2	ARG	37	37.479	-36.189	35.186	1.00	145.27	B
1377	C	ARG	37	42.759	-30.509	31.432	1.00	79.44	B
1378	O	ARG	37	42.839	-29.617	32.307	1.00	74.93	B
1379	N	MET	38	43.735	-30.781	30.563	1.00	53.69	B
1380	CA	MET	38	44.970	-30.030	30.644	1.00	51.02	B
1381	CB	MET	38	46.182	-30.939	30.328	1.00	70.24	B
1382	CG	MET	38	47.181	-30.913	31.561	1.00	52.68	B
1383	SD	MET	38	48.736	-31.245	30.977	1.00	87.26	B
1384	CE	MET	38	49.652	-29.833	31.177	1.00	82.46	B
1385	C	MET	38	44.969	-28.792	29.782	1.00	76.35	B
1386	O	MET	38	45.951	-28.081	29.715	1.00	89.28	B
1387	N	ALA	39	43.863	-28.527	29.109	1.00	85.08	B
1388	CA	ALA	39	43.788	-27.352	28.260	1.00	86.29	B
1389	CB	ALA	39	43.429	-27.711	26.838	1.00	106.92	B
1390	C	ALA	39	42.716	-26.520	28.893	1.00	65.03	B
1391	O	ALA	39	42.635	-25.323	28.635	1.00	98.07	B
1392	N	GLU	40	41.927	-27.172	29.742	1.00	56.42	B
1393	CA	GLU	40	40.921	-26.493	30.517	1.00	49.53	B
1394	CB	GLU	40	39.893	-27.496	31.041	1.00	42.68	B
1395	CG	GLU	40	38.575	-26.820	31.603	1.00	83.75	B
1396	CD	GLU	40	37.614	-27.774	32.340	1.00	139.18	B
1397	OE1	GLU	40	38.086	-28.828	32.862	1.00	142.43	B
1398	OE2	GLU	40	36.390	-27.442	32.406	1.00	134.43	B
1399	C	GLU	40	41.607	-25.777	31.732	1.00	76.88	B
1400	O	GLU	40	40.954	-25.239	32.616	1.00	69.42	B
1401	N	ALA	41	42.925	-25.780	31.766	1.00	77.57	B
1402	CA	ALA	41	43.664	-25.160	32.836	1.00	77.30	B
1403	CB	ALA	41	44.281	-26.252	33.681	1.00	54.02	B
1404	C	ALA	41	44.737	-24.264	32.182	1.00	91.69	B
1405	O	ALA	41	45.760	-23.891	32.771	1.00	75.89	B
1406	N	GLY	42	44.495	-23.959	30.920	1.00	77.47	B
1407	CA	GLY	42	45.344	-23.048	30.169	1.00	43.36	B
1408	C	GLY	42	46.557	-23.657	29.577	1.00	49.13	B
1409	O	GLY	42	47.403	-22.898	29.080	1.00	71.15	B
1410	N	PHE	43	46.666	-24.990	29.570	1.00	49.94	B

1411	CA	PHE	43	47.912	-25.496	29.004	1.00	52.22	B
1412	CB	PHE	43	48.349	-26.780	29.716	1.00	49.78	B
1413	CG	PHE	43	48.725	-26.553	31.122	1.00	81.13	B
1414	CD1	PHE	43	47.805	-26.756	32.134	1.00	65.79	B
1415	CD2	PHE	43	49.996	-26.077	31.448	1.00	71.90	B
1416	CE1	PHE	43	48.130	-26.492	33.478	1.00	72.69	B
1417	CE2	PHE	43	50.331	-25.811	32.759	1.00	61.13	B
1418	CZ	PHE	43	49.380	-26.023	33.795	1.00	66.99	B
1419	C	PHE	43	47.959	-25.673	27.474	1.00	71.63	B
1420	O	PHE	43	46.975	-25.928	26.776	1.00	46.52	B
1421	N	ILE	44	49.152	-25.497	26.984	1.00	61.71	B
1422	CA	ILE	44	49.455	-25.653	25.598	1.00	60.12	B
1423	CB	ILE	44	49.808	-24.268	25.003	1.00	61.37	B
1424	CG2	ILE	44	50.870	-24.416	23.993	1.00	61.96	B
1425	CG1	ILE	44	48.522	-23.572	24.526	1.00	69.76	B
1426	CD1	ILE	44	48.651	-22.055	24.413	1.00	101.30	B
1427	C	ILE	44	50.703	-26.596	25.593	1.00	93.60	B
1428	O	ILE	44	51.635	-26.419	26.413	1.00	82.62	B
1429	N	HIS	45	50.708	-27.597	24.701	1.00	70.01	B
1430	CA	HIS	45	51.812	-28.553	24.609	1.00	91.04	B
1431	CB	HIS	45	51.331	-29.832	23.899	1.00	85.90	B
1432	CG	HIS	45	52.272	-30.988	24.016	1.00	91.06	B
1433	CD2	HIS	45	53.392	-31.162	24.763	1.00	96.23	B
1434	ND1	HIS	45	52.114	-32.146	23.283	1.00	100.45	B
1435	CE1	HIS	45	53.098	-32.979	23.566	1.00	122.08	B
1436	NE2	HIS	45	53.887	-32.407	24.463	1.00	114.96	B
1437	C	HIS	45	52.991	-27.919	23.858	1.00	77.32	B
1438	O	HIS	45	52.861	-27.558	22.697	1.00	120.90	B
1439	N	CYS	46	54.128	-27.769	24.531	1.00	80.34	B
1440	CA	CYS	46	55.319	-27.177	23.932	1.00	71.16	B
1441	CB	CYS	46	55.706	-25.925	24.710	1.00	102.35	B
1442	SG	CYS	46	54.352	-24.937	25.360	1.00	107.76	B
1443	C	CYS	46	56.436	-28.232	24.058	1.00	95.37	B
1444	O	CYS	46	57.480	-28.008	24.742	1.00	82.79	B
1445	N	PRO	47	56.235	-29.404	23.395	1.00	105.82	B
1446	CD	PRO	47	55.091	-29.700	22.507	1.00	97.63	B
1447	CA	PRO	47	57.175	-30.533	23.405	1.00	78.73	B
1448	CB	PRO	47	56.402	-31.642	22.692	1.00	96.16	B
1449	CG	PRO	47	55.573	-30.889	21.722	1.00	103.72	B
1450	C	PRO	47	58.505	-30.257	22.768	1.00	86.31	B
1451	O	PRO	47	58.617	-29.454	21.829	1.00	98.74	B
1452	N	THR	48	59.521	-30.939	23.275	1.00	96.47	B
1453	CA	THR	48	60.842	-30.757	22.753	1.00	105.10	B
1454	CB	THR	48	61.514	-29.624	23.556	1.00	98.95	B
1455	OG1	THR	48	62.858	-29.959	23.888	1.00	110.39	B
1456	CG2	THR	48	60.738	-29.354	24.793	1.00	100.47	B
1457	C	THR	48	61.569	-32.094	22.780	1.00	120.94	B
1458	O	THR	48	60.918	-33.132	22.774	1.00	130.65	B
1459	N	GLU	49	62.899	-32.077	22.756	1.00	143.31	B
1460	CA	GLU	49	63.702	-33.301	22.780	1.00	147.74	B
1461	CB	GLU	49	65.115	-32.991	22.278	1.00	159.77	B

1462	CG	GLU	49	65.132	-32.558	20.832	1.00	160.37	B
1463	CD	GLU	49	64.463	-33.585	19.936	1.00	162.74	B
1464	OE1	GLU	49	63.223	-33.778	20.035	1.00	147.73	B
1465	OE2	GLU	49	65.189	-34.211	19.137	1.00	168.44	B
1466	C	GLU	49	63.773	-33.905	24.182	1.00	141.80	B
1467	O	GLU	49	63.436	-35.076	24.385	1.00	105.37	B
1468	N	ASN	50	64.212	-33.084	25.136	1.00	134.61	B
1469	CA	ASN	50	64.358	-33.475	26.535	1.00	116.14	B
1470	CB	ASN	50	65.603	-32.802	27.147	1.00	128.63	B
1471	CG	ASN	50	66.654	-32.376	26.085	1.00	144.23	B
1472	OD1	ASN	50	66.950	-33.118	25.133	1.00	139.45	B
1473	ND2	ASN	50	67.229	-31.176	26.268	1.00	136.41	B
1474	C	ASN	50	63.119	-33.071	27.335	1.00	119.69	B
1475	O	ASN	50	63.145	-33.045	28.580	1.00	120.60	B
1476	N	GLU	51	62.044	-32.746	26.612	1.00	125.19	B
1477	CA	GLU	51	60.798	-32.330	27.239	1.00	111.62	B
1478	CB	GLU	51	60.861	-30.823	27.534	1.00	119.12	B
1479	CG	GLU	51	62.147	-30.303	28.204	1.00	90.04	B
1480	CD	GLU	51	63.113	-29.642	27.225	1.00	114.16	B
1481	OE1	GLU	51	62.741	-28.660	26.549	1.00	109.61	B
1482	OE2	GLU	51	64.267	-30.102	27.131	1.00	114.29	B
1483	C	GLU	51	59.529	-32.628	26.407	1.00	104.22	B
1484	O	GLU	51	58.620	-31.807	26.365	1.00	100.20	B
1485	N	PRO	52	59.437	-33.815	25.764	1.00	110.14	B
1486	CD	PRO	52	60.403	-34.917	25.917	1.00	124.48	B
1487	CA	PRO	52	58.294	-34.245	24.927	1.00	98.42	B
1488	CB	PRO	52	58.644	-35.687	24.563	1.00	114.27	B
1489	CG	PRO	52	59.541	-36.141	25.705	1.00	104.46	B
1490	C	PRO	52	56.927	-34.167	25.560	1.00	95.47	B
1491	O	PRO	52	55.926	-34.341	24.860	1.00	86.88	B
1492	N	ASP	53	56.899	-33.946	26.880	1.00	97.78	B
1493	CA	ASP	53	55.663	-33.825	27.666	1.00	104.38	B
1494	CB	ASP	53	55.629	-34.886	28.789	1.00	116.26	B
1495	CG	ASP	53	56.393	-34.435	30.091	1.00	139.93	B
1496	OD1	ASP	53	55.948	-34.801	31.218	1.00	107.40	B
1497	OD2	ASP	53	57.439	-33.728	30.003	1.00	106.00	B
1498	C	ASP	53	55.503	-32.413	28.309	1.00	110.87	B
1499	O	ASP	53	54.636	-32.205	29.172	1.00	87.42	B
1500	N	MET	54	56.313	-31.435	27.903	1.00	69.31	B
1501	CA	MET	54	56.208	-30.108	28.501	1.00	90.89	B
1502	CB	MET	54	57.487	-29.342	28.252	1.00	100.64	B
1503	CG	MET	54	57.538	-28.116	29.060	1.00	75.98	B
1504	SD	MET	54	59.017	-27.282	28.968	1.00	135.79	B
1505	CE	MET	54	60.034	-28.316	30.009	1.00	109.88	B
1506	C	MET	54	55.023	-29.210	28.108	1.00	94.14	B
1507	O	MET	54	54.787	-28.901	26.941	1.00	105.65	B
1508	N	ALA	55	54.300	-28.755	29.117	1.00	92.77	B
1509	CA	ALA	55	53.171	-27.885	28.879	1.00	82.80	B
1510	CB	ALA	55	51.977	-28.427	29.592	1.00	102.10	B
1511	C	ALA	55	53.449	-26.435	29.329	1.00	101.09	B
1512	O	ALA	55	54.519	-26.133	29.833	1.00	85.50	B

1513	N	GLN	56	52.483	-25.543	29.128	1.00	95.42	B
1514	CA	GLN	56	52.634	-24.143	29.516	1.00	62.30	B
1515	CB	GLN	56	53.481	-23.419	28.525	1.00	65.03	B
1516	CG	GLN	56	53.666	-21.958	28.845	1.00	67.98	B
1517	CD	GLN	56	54.719	-21.382	27.941	1.00	85.05	B
1518	OE1	GLN	56	54.780	-21.761	26.761	1.00	89.78	B
1519	NE2	GLN	56	55.586	-20.487	28.483	1.00	60.22	B
1520	C	GLN	56	51.303	-23.469	29.583	1.00	56.11	B
1521	O	GLN	56	50.370	-23.936	28.904	1.00	83.77	B
1522	N	CYS	57	51.182	-22.412	30.416	1.00	68.61	B
1523	CA	CYS	57	49.895	-21.619	30.530	1.00	62.69	B
1524	C	CYS	57	49.952	-20.688	29.282	1.00	76.91	B
1525	O	CYS	57	51.042	-20.315	28.836	1.00	67.10	B
1526	CB	CYS	57	49.976	-20.663	31.636	1.00	50.58	B
1527	SG	CYS	57	48.774	-20.186	32.916	1.00	70.90	B
1528	N	PHE	58	48.821	-20.300	28.713	1.00	64.80	B
1529	CA	PHE	58	48.947	-19.428	27.569	1.00	90.57	B
1530	CB	PHE	58	47.746	-19.514	26.609	1.00	55.74	B
1531	CG	PHE	58	46.460	-18.955	27.187	1.00	36.53	B
1532	CD1	PHE	58	45.911	-17.685	26.738	1.00	47.27	B
1533	CD2	PHE	58	45.765	-19.729	28.118	1.00	38.34	B
1534	CE1	PHE	58	44.653	-17.241	27.256	1.00	37.44	B
1535	CE2	PHE	58	44.504	-19.323	28.640	1.00	40.42	B
1536	CZ	PHE	58	43.946	-18.069	28.206	1.00	54.79	B
1537	C	PHE	58	49.015	-18.074	28.195	1.00	66.01	B
1538	O	PHE	58	49.689	-17.242	27.664	1.00	75.02	B
1539	N	PHE	59	48.367	-17.926	29.360	1.00	77.46	B
1540	CA	PHE	59	48.275	-16.670	30.112	1.00	76.07	B
1541	CB	PHE	59	46.992	-16.676	30.913	1.00	61.25	B
1542	CG	PHE	59	46.571	-15.304	31.380	1.00	94.32	B
1543	CD1	PHE	59	45.280	-14.833	31.123	1.00	72.96	B
1544	CD2	PHE	59	47.439	-14.500	32.111	1.00	63.11	B
1545	CE1	PHE	59	44.849	-13.614	31.593	1.00	73.95	B
1546	CE2	PHE	59	47.002	-13.263	32.578	1.00	71.44	B
1547	CZ	PHE	59	45.713	-12.821	32.327	1.00	72.92	B
1548	C	PHE	59	49.386	-16.220	31.048	1.00	79.58	B
1549	O	PHE	59	49.918	-15.081	30.941	1.00	75.25	B
1550	N	CYS	60	49.679	-17.084	32.007	1.00	77.41	B
1551	CA	CYS	60	50.725	-16.835	33.034	1.00	84.59	B
1552	C	CYS	60	52.094	-17.253	32.543	1.00	74.44	B
1553	O	CYS	60	53.089	-16.705	32.972	1.00	75.89	B
1554	CB	CYS	60	50.439	-17.616	34.368	1.00	89.78	B
1555	SG	CYS	60	50.250	-19.478	34.362	1.00	60.28	B
1556	N	PHE	61	52.133	-18.221	31.626	1.00	78.93	B
1557	CA	PHE	61	53.395	-18.737	31.054	1.00	73.90	B
1558	CB	PHE	61	54.312	-17.603	30.630	1.00	66.00	B
1559	CG	PHE	61	53.722	-16.736	29.556	1.00	92.82	B
1560	CD1	PHE	61	52.781	-15.729	29.863	1.00	63.57	B
1561	CD2	PHE	61	54.023	-16.976	28.236	1.00	70.57	B
1562	CE1	PHE	61	52.168	-15.013	28.889	1.00	64.66	B
1563	CE2	PHE	61	53.399	-16.238	27.246	1.00	66.99	B

1564	CZ	PHE	61	52.481	-15.271	27.565	1.00	78.96	B
1565	C	PHE	61	54.203	-19.731	31.888	1.00	105.01	B
1566	O	PHE	61	55.323	-20.092	31.493	1.00	66.93	B
1567	N	LYS	62	53.685	-20.199	33.024	1.00	76.72	B
1568	CA	LYS	62	54.509	-21.133	33.734	1.00	78.16	B
1569	CB	LYS	62	53.911	-21.400	35.106	1.00	81.32	B
1570	CG	LYS	62	54.838	-22.218	35.952	1.00	81.42	B
1571	CD	LYS	62	55.298	-21.405	37.149	1.00	134.32	B
1572	CE	LYS	62	56.360	-22.113	38.005	1.00	120.73	B
1573	NZ	LYS	62	56.475	-21.437	39.364	1.00	107.55	B
1574	C	LYS	62	54.590	-22.433	32.909	1.00	85.41	B
1575	O	LYS	62	53.575	-22.882	32.353	1.00	88.95	B
1576	N	GLU	63	55.804	-22.986	32.800	1.00	73.07	B
1577	CA	GLU	63	56.079	-24.266	32.122	1.00	82.52	B
1578	CB	GLU	63	57.394	-24.173	31.329	1.00	76.47	B
1579	CG	GLU	63	57.401	-23.025	30.304	1.00	84.65	B
1580	CD	GLU	63	58.659	-22.934	29.443	1.00	106.36	B
1581	OE1	GLU	63	58.833	-23.767	28.510	1.00	95.94	B
1582	OE2	GLU	63	59.465	-22.010	29.705	1.00	94.81	B
1583	C	GLU	63	56.165	-25.448	33.152	1.00	103.71	B
1584	O	GLU	63	56.796	-25.341	34.205	1.00	88.53	B
1585	N	LEU	64	55.528	-26.577	32.851	1.00	88.50	B
1586	CA	LEU	64	55.530	-27.721	33.762	1.00	59.33	B
1587	CB	LEU	64	54.170	-27.819	34.461	1.00	57.66	B
1588	CG	LEU	64	53.952	-26.971	35.710	1.00	58.16	B
1589	CD1	LEU	64	54.666	-25.658	35.724	1.00	69.19	B
1590	CD2	LEU	64	52.483	-26.771	35.816	1.00	50.11	B
1591	C	LEU	64	55.810	-29.061	33.077	1.00	94.32	B
1592	O	LEU	64	55.149	-29.399	32.100	1.00	95.01	B
1593	N	GLU	65	56.762	-29.819	33.647	1.00	107.45	B
1594	CA	GLU	65	57.233	-31.124	33.153	1.00	85.85	B
1595	CB	GLU	65	58.763	-31.114	33.062	1.00	80.20	B
1596	CG	GLU	65	59.358	-32.232	32.171	1.00	124.75	B
1597	CD	GLU	65	60.728	-31.857	31.572	1.00	132.25	B
1598	OE1	GLU	65	61.425	-31.050	32.244	1.00	128.09	B
1599	OE2	GLU	65	61.093	-32.365	30.456	1.00	115.08	B
1600	C	GLU	65	56.830	-32.264	34.065	1.00	93.31	B
1601	O	GLU	65	56.177	-32.062	35.079	1.00	103.75	B
1602	N	GLY	66	57.227	-33.477	33.718	1.00	97.38	B
1603	CA	GLY	66	56.899	-34.598	34.580	1.00	95.98	B
1604	C	GLY	66	55.441	-34.745	34.934	1.00	97.47	B
1605	O	GLY	66	55.018	-34.520	36.070	1.00	105.21	B
1606	N	TRP	67	54.660	-35.142	33.945	1.00	100.63	B
1607	CA	TRP	67	53.234	-35.320	34.135	1.00	84.99	B
1608	CB	TRP	67	52.484	-34.817	32.868	1.00	77.55	B
1609	CG	TRP	67	52.467	-33.286	32.780	1.00	94.77	B
1610	CD2	TRP	67	51.545	-32.412	33.492	1.00	48.83	B
1611	CE2	TRP	67	52.086	-31.080	33.400	1.00	48.25	B
1612	CE3	TRP	67	50.345	-32.597	34.204	1.00	64.08	B
1613	CD1	TRP	67	53.469	-32.467	32.284	1.00	68.98	B
1614	NE1	TRP	67	53.246	-31.152	32.663	1.00	57.82	B

1615	CZ2	TRP	67	51.446	-29.946	34.005	1.00	70.25	B
1616	CZ3	TRP	67	49.704	-31.466	34.806	1.00	69.43	B
1617	CH2	TRP	67	50.276	-30.161	34.698	1.00	67.30	B
1618	C	TRP	67	53.013	-36.810	34.356	1.00	97.10	B
1619	O	TRP	67	53.744	-37.625	33.798	1.00	72.27	B
1620	N	GLU	68	52.027	-37.161	35.182	1.00	83.26	B
1621	CA	GLU	68	51.659	-38.558	35.437	1.00	89.14	B
1622	CB	GLU	68	52.194	-39.049	36.787	1.00	140.75	B
1623	CG	GLU	68	53.715	-38.936	36.968	1.00	148.55	B
1624	CD	GLU	68	54.197	-39.640	38.243	1.00	149.85	B
1625	OE1	GLU	68	53.626	-39.378	39.334	1.00	137.96	B
1626	OE2	GLU	68	55.147	-40.451	38.149	1.00	130.51	B
1627	C	GLU	68	50.126	-38.658	35.408	1.00	103.72	B
1628	O	GLU	68	49.399	-37.787	35.928	1.00	77.62	B
1629	N	PRO	69	49.624	-39.753	34.823	1.00	113.49	B
1630	CD	PRO	69	50.450	-40.969	34.746	1.00	91.81	B
1631	CA	PRO	69	48.216	-40.091	34.635	1.00	96.98	B
1632	CB	PRO	69	48.223	-41.627	34.593	1.00	97.07	B
1633	CG	PRO	69	49.529	-41.930	34.032	1.00	87.00	B
1634	C	PRO	69	47.255	-39.581	35.679	1.00	106.75	B
1635	O	PRO	69	46.075	-39.287	35.371	1.00	117.83	B
1636	N	ASP	70	47.748	-39.455	36.906	1.00	86.61	B
1637	CA	ASP	70	46.848	-39.098	37.994	1.00	86.99	B
1638	CB	ASP	70	47.098	-40.032	39.196	1.00	135.85	B
1639	CG	ASP	70	46.717	-41.503	38.887	1.00	130.51	B
1640	OD1	ASP	70	45.532	-41.923	38.993	1.00	100.94	B
1641	OD2	ASP	70	47.621	-42.252	38.493	1.00	131.73	B
1642	C	ASP	70	46.834	-37.664	38.395	1.00	84.73	B
1643	O	ASP	70	45.921	-37.235	39.162	1.00	74.28	B
1644	N	ASP	71	47.837	-36.952	37.862	1.00	90.95	B
1645	CA	ASP	71	48.061	-35.486	38.014	1.00	79.92	B
1646	CB	ASP	71	49.229	-35.049	37.095	1.00	70.08	B
1647	CG	ASP	71	50.622	-35.430	37.624	1.00	70.14	B
1648	OD1	ASP	71	50.732	-35.690	38.843	1.00	115.70	B
1649	OD2	ASP	71	51.623	-35.414	36.823	1.00	86.65	B
1650	C	ASP	71	46.784	-34.663	37.581	1.00	78.16	B
1651	O	ASP	71	46.288	-34.794	36.446	1.00	80.99	B
1652	N	ASP	72	46.256	-33.834	38.476	1.00	88.86	B
1653	CA	ASP	72	45.104	-32.971	38.159	1.00	91.35	B
1654	CB	ASP	72	44.255	-32.792	39.416	1.00	96.62	B
1655	CG	ASP	72	43.131	-31.775	39.245	1.00	98.06	B
1656	OD1	ASP	72	42.344	-31.928	38.293	1.00	119.84	B
1657	OD2	ASP	72	43.034	-30.839	40.072	1.00	128.14	B
1658	C	ASP	72	45.722	-31.618	37.700	1.00	86.13	B
1659	O	ASP	72	46.177	-30.821	38.509	1.00	91.48	B
1660	N	PRO	73	45.710	-31.341	36.390	1.00	104.32	B
1661	CD	PRO	73	44.680	-31.854	35.474	1.00	78.55	B
1662	CA	PRO	73	46.296	-30.100	35.857	1.00	98.11	B
1663	CB	PRO	73	45.940	-30.135	34.366	1.00	74.25	B
1664	CG	PRO	73	45.273	-31.499	34.146	1.00	75.98	B
1665	C	PRO	73	45.872	-28.784	36.530	1.00	76.58	B

1666	O	PRO	73	46.713	-27.910	36.740	1.00	60.80	B
1667	N	ILE	74	44.595	-28.607	36.856	1.00	62.13	B
1668	CA	ILE	74	44.185	-27.376	37.553	1.00	60.59	B
1669	CB	ILE	74	42.718	-27.391	37.904	1.00	66.71	B
1670	CG2	ILE	74	42.348	-26.094	38.661	1.00	76.95	B
1671	CG1	ILE	74	41.917	-27.545	36.610	1.00	90.80	B
1672	CD1	ILE	74	40.411	-27.499	36.790	1.00	70.00	B
1673	C	ILE	74	44.966	-27.209	38.853	1.00	91.53	B
1674	O	ILE	74	45.550	-26.151	39.121	1.00	99.65	B
1675	N	GLU	75	44.961	-28.272	39.656	1.00	102.16	B
1676	CA	GLU	75	45.699	-28.290	40.909	1.00	73.59	B
1677	CB	GLU	75	45.456	-29.615	41.635	1.00	106.26	B
1678	CG	GLU	75	44.254	-29.490	42.582	1.00	139.19	B
1679	CD	GLU	75	44.162	-28.080	43.284	1.00	162.09	B
1680	OE1	GLU	75	45.216	-27.457	43.605	1.00	146.97	B
1681	OE2	GLU	75	43.026	-27.601	43.534	1.00	158.56	B
1682	C	GLU	75	47.193	-28.019	40.707	1.00	73.37	B
1683	O	GLU	75	47.770	-27.150	41.369	1.00	81.60	B
1684	N	GLU	76	47.830	-28.751	39.792	1.00	45.72	B
1685	CA	GLU	76	49.242	-28.466	39.519	1.00	49.32	B
1686	CB	GLU	76	49.745	-29.330	38.340	1.00	51.46	B
1687	CG	GLU	76	49.837	-30.834	38.647	1.00	112.81	B
1688	CD	GLU	76	50.505	-31.104	39.994	1.00	123.93	B
1689	OE1	GLU	76	51.699	-30.771	40.167	1.00	122.64	B
1690	OE2	GLU	76	49.822	-31.632	40.888	1.00	83.88	B
1691	C	GLU	76	49.453	-26.990	39.167	1.00	83.88	B
1692	O	GLU	76	50.495	-26.381	39.494	1.00	75.71	B
1693	N	HIS	77	48.450	-26.434	38.482	1.00	69.22	B
1694	CA	HIS	77	48.522	-25.079	38.032	1.00	80.17	B
1695	CB	HIS	77	47.474	-24.839	36.944	1.00	90.91	B
1696	CG	HIS	77	47.655	-23.552	36.190	1.00	95.63	B
1697	CD2	HIS	77	48.775	-22.865	35.808	1.00	68.79	B
1698	ND1	HIS	77	46.592	-22.735	35.880	1.00	68.96	B
1699	CE1	HIS	77	47.036	-21.598	35.364	1.00	73.30	B
1700	NE2	HIS	77	48.359	-21.653	35.314	1.00	79.20	B
1701	C	HIS	77	48.409	-24.092	39.197	1.00	77.17	B
1702	O	HIS	77	49.240	-23.198	39.283	1.00	71.26	B
1703	N	LYS	78	47.432	-24.286	40.089	1.00	74.62	B
1704	CA	LYS	78	47.214	-23.439	41.295	1.00	74.10	B
1705	CB	LYS	78	45.991	-23.890	42.127	1.00	57.57	B
1706	CG	LYS	78	44.599	-23.422	41.704	1.00	100.79	B
1707	CD	LYS	78	43.525	-24.071	42.593	1.00	73.20	B
1708	CE	LYS	78	42.107	-23.450	42.386	1.00	105.50	B
1709	NZ	LYS	78	41.000	-24.002	43.296	1.00	97.74	B
1710	C	LYS	78	48.392	-23.507	42.254	1.00	93.20	B
1711	O	LYS	78	48.681	-22.528	42.977	1.00	117.83	B
1712	N	LYS	79	49.055	-24.664	42.275	1.00	82.30	B
1713	CA	LYS	79	50.174	-24.871	43.168	1.00	97.37	B
1714	CB	LYS	79	50.003	-26.204	43.899	1.00	114.67	B
1715	CG	LYS	79	48.989	-26.122	45.047	1.00	137.03	B
1716	CD	LYS	79	49.451	-26.984	46.230	1.00	153.58	B

1717	CE	LYS	79	48.832	-26.582	47.582	1.00	121.88	B
1718	NZ	LYS	79	49.486	-27.404	48.660	1.00	118.41	B
1719	C	LYS	79	51.512	-24.816	42.483	1.00	91.15	B
1720	O	LYS	79	52.404	-25.636	42.750	1.00	103.44	B
1721	N	HIS	80	51.636	-23.834	41.598	1.00	91.54	B
1722	CA	HIS	80	52.834	-23.583	40.797	1.00	86.06	B
1723	CB	HIS	80	53.000	-24.658	39.752	1.00	77.83	B
1724	CG	HIS	80	53.754	-25.838	40.236	1.00	98.39	B
1725	CD2	HIS	80	53.369	-27.114	40.481	1.00	95.94	B
1726	ND1	HIS	80	55.109	-25.800	40.484	1.00	88.97	B
1727	CE1	HIS	80	55.525	-26.999	40.848	1.00	94.38	B
1728	NE2	HIS	80	54.477	-27.815	40.850	1.00	117.19	B
1729	C	HIS	80	52.713	-22.205	40.141	1.00	100.09	B
1730	O	HIS	80	53.669	-21.704	39.529	1.00	95.55	B
1731	N	SER	81	51.537	-21.600	40.301	1.00	84.44	B
1732	CA	SER	81	51.231	-20.274	39.808	1.00	76.97	B
1733	CB	SER	81	51.032	-20.284	38.301	1.00	96.91	B
1734	OG	SER	81	51.281	-18.994	37.802	1.00	81.74	B
1735	C	SER	81	49.949	-19.897	40.516	1.00	83.10	B
1736	O	SER	81	48.881	-20.387	40.207	1.00	117.86	B
1737	N	SER	82	50.049	-19.047	41.506	1.00	111.65	B
1738	CA	SER	82	48.863	-18.708	42.232	1.00	105.66	B
1739	CB	SER	82	49.219	-18.588	43.701	1.00	131.97	B
1740	OG	SER	82	48.074	-18.263	44.444	1.00	161.28	B
1741	C	SER	82	48.366	-17.399	41.681	1.00	104.66	B
1742	O	SER	82	47.181	-17.099	41.783	1.00	87.43	B
1743	N	GLY	83	49.301	-16.643	41.087	1.00	131.36	B
1744	CA	GLY	83	49.033	-15.328	40.510	1.00	137.21	B
1745	C	GLY	83	48.840	-15.404	39.007	1.00	128.34	B
1746	O	GLY	83	49.664	-14.981	38.167	1.00	124.76	B
1747	N	CYS	84	47.723	-15.995	38.660	1.00	100.57	B
1748	CA	CYS	84	47.414	-16.147	37.294	1.00	80.62	B
1749	CB	CYS	84	47.744	-17.556	36.895	1.00	105.20	B
1750	SG	CYS	84	46.799	-17.903	35.459	1.00	85.79	B
1751	C	CYS	84	45.935	-15.826	37.169	1.00	86.78	B
1752	O	CYS	84	45.086	-16.618	37.568	1.00	76.13	B
1753	N	ALA	85	45.639	-14.642	36.631	1.00	86.49	B
1754	CA	ALA	85	44.269	-14.190	36.494	1.00	82.09	B
1755	CB	ALA	85	44.228	-12.948	35.668	1.00	107.11	B
1756	C	ALA	85	43.372	-15.241	35.893	1.00	71.03	B
1757	O	ALA	85	42.211	-15.337	36.269	1.00	73.36	B
1758	N	PHE	86	43.919	-16.037	34.975	1.00	67.86	B
1759	CA	PHE	86	43.168	-17.089	34.300	1.00	57.40	B
1760	CB	PHE	86	44.093	-17.925	33.435	1.00	69.88	B
1761	CG	PHE	86	43.380	-18.882	32.561	1.00	97.51	B
1762	CD1	PHE	86	42.492	-18.415	31.618	1.00	90.12	B
1763	CD2	PHE	86	43.556	-20.236	32.697	1.00	94.83	B
1764	CE1	PHE	86	41.774	-19.268	30.826	1.00	91.58	B
1765	CE2	PHE	86	42.841	-21.097	31.901	1.00	98.39	B
1766	CZ	PHE	86	41.944	-20.607	30.964	1.00	94.16	B
1767	C	PHE	86	42.388	-17.994	35.219	1.00	62.38	B

1768	O	PHE	86	41.162	-18.166	35.061	1.00	59.75	B
1769	N	LEU	87	43.062	-18.565	36.204	1.00	74.34	B
1770	CA	LEU	87	42.389	-19.460	37.144	1.00	73.87	B
1771	CB	LEU	87	43.351	-19.902	38.234	1.00	87.60	B
1772	CG	LEU	87	44.481	-20.705	37.608	1.00	100.72	B
1773	CD1	LEU	87	45.700	-20.684	38.514	1.00	72.94	B
1774	CD2	LEU	87	43.990	-22.091	37.342	1.00	87.93	B
1775	C	LEU	87	41.134	-18.842	37.748	1.00	72.60	B
1776	O	LEU	87	40.155	-19.575	38.010	1.00	87.79	B
1777	N	SER	88	41.119	-17.512	37.941	1.00	83.36	B
1778	CA	SER	88	39.911	-16.855	38.491	1.00	86.42	B
1779	CB	SER	88	40.314	-15.573	39.190	1.00	62.88	B
1780	OG	SER	88	41.694	-15.360	38.991	1.00	90.74	B
1781	C	SER	88	38.793	-16.599	37.439	1.00	66.68	B
1782	O	SER	88	37.634	-16.350	37.784	1.00	70.14	B
1783	N	VAL	89	39.136	-16.709	36.158	1.00	81.91	B
1784	CA	VAL	89	38.174	-16.554	35.061	1.00	78.83	B
1785	CB	VAL	89	38.875	-16.506	33.699	1.00	91.16	B
1786	CG1	VAL	89	37.881	-16.649	32.605	1.00	85.09	B
1787	CG2	VAL	89	39.625	-15.214	33.519	1.00	64.13	B
1788	C	VAL	89	37.215	-17.732	35.029	1.00	77.56	B
1789	O	VAL	89	37.553	-18.842	34.557	1.00	71.82	B
1790	N	LYS	90	36.018	-17.439	35.514	1.00	61.10	B
1791	CA	LYS	90	34.910	-18.363	35.625	1.00	93.09	B
1792	CB	LYS	90	34.107	-18.000	36.886	1.00	102.55	B
1793	CG	LYS	90	34.971	-17.793	38.175	1.00	123.61	B
1794	CD	LYS	90	35.721	-19.065	38.613	1.00	137.64	B
1795	CE	LYS	90	36.628	-18.832	39.835	1.00	129.28	B
1796	NZ	LYS	90	37.252	-20.109	40.361	1.00	133.48	B
1797	C	LYS	90	33.977	-18.396	34.394	1.00	107.94	B
1798	O	LYS	90	33.366	-19.429	34.093	1.00	92.75	B
1799	N	LYS	91	33.868	-17.275	33.682	1.00	107.14	B
1800	CA	LYS	91	32.996	-17.179	32.506	1.00	81.66	B
1801	CB	LYS	91	32.703	-15.719	32.172	1.00	69.65	B
1802	CG	LYS	91	31.640	-15.122	33.007	1.00	88.94	B
1803	CD	LYS	91	31.698	-13.638	32.921	1.00	79.44	B
1804	CE	LYS	91	30.895	-13.045	34.063	1.00	113.81	B
1805	NZ	LYS	91	31.063	-11.566	34.183	1.00	121.40	B
1806	C	LYS	91	33.508	-17.859	31.248	1.00	100.58	B
1807	O	LYS	91	34.720	-18.011	31.020	1.00	76.27	B
1808	N	GLN	92	32.569	-18.293	30.425	1.00	94.37	B
1809	CA	GLN	92	32.963	-18.919	29.178	1.00	101.61	B
1810	CB	GLN	92	31.733	-19.553	28.532	1.00	109.36	B
1811	CG	GLN	92	31.527	-20.999	28.924	1.00	121.00	B
1812	CD	GLN	92	32.625	-21.887	28.336	1.00	132.49	B
1813	OE1	GLN	92	33.829	-21.633	28.526	1.00	127.02	B
1814	NE2	GLN	92	32.214	-22.928	27.607	1.00	119.69	B
1815	C	GLN	92	33.546	-17.799	28.311	1.00	88.93	B
1816	O	GLN	92	33.198	-16.620	28.486	1.00	75.87	B
1817	N	PHE	93	34.431	-18.139	27.382	1.00	83.07	B
1818	CA	PHE	93	35.033	-17.117	26.528	1.00	84.94	B

1819	CB	PHE	93	35.711	-17.764	25.338	1.00	67.80	B
1820	CG	PHE	93	36.435	-16.800	24.495	1.00	62.43	B
1821	CD1	PHE	93	37.728	-16.429	24.802	1.00	88.87	B
1822	CD2	PHE	93	35.848	-16.297	23.337	1.00	94.90	B
1823	CE1	PHE	93	38.459	-15.560	23.942	1.00	79.29	B
1824	CE2	PHE	93	36.559	-15.441	22.473	1.00	87.11	B
1825	CZ	PHE	93	37.883	-15.072	22.779	1.00	58.99	B
1826	C	PHE	93	33.983	-16.117	26.028	1.00	105.57	B
1827	O	PHE	93	33.985	-14.911	26.390	1.00	94.48	B
1828	N	GLU	94	33.064	-16.659	25.230	1.00	85.86	B
1829	CA	GLU	94	31.997	-15.891	24.632	1.00	74.46	B
1830	CB	GLU	94	31.179	-16.792	23.692	1.00	86.38	B
1831	CG	GLU	94	32.051	-17.341	22.540	1.00	111.00	B
1832	CD	GLU	94	31.254	-17.788	21.309	1.00	130.58	B
1833	OE1	GLU	94	31.885	-18.225	20.300	1.00	127.70	B
1834	OE2	GLU	94	30.001	-17.694	21.349	1.00	117.55	B
1835	C	GLU	94	31.079	-15.127	25.575	1.00	71.85	B
1836	O	GLU	94	30.302	-14.312	25.105	1.00	75.74	B
1837	N	GLU	95	31.151	-15.344	26.887	1.00	79.46	B
1838	CA	GLU	95	30.253	-14.617	27.780	1.00	65.11	B
1839	CB	GLU	95	29.658	-15.583	28.809	1.00	88.22	B
1840	CG	GLU	95	28.902	-14.952	30.010	1.00	113.68	B
1841	CD	GLU	95	27.918	-13.800	29.640	1.00	122.00	B
1842	OE1	GLU	95	26.713	-14.087	29.378	1.00	119.23	B
1843	OE2	GLU	95	28.356	-12.601	29.618	1.00	84.54	B
1844	C	GLU	95	31.046	-13.463	28.420	1.00	62.78	B
1845	O	GLU	95	30.566	-12.695	29.278	1.00	66.44	B
1846	N	LEU	96	32.307	-13.381	28.013	1.00	48.85	B
1847	CA	LEU	96	33.201	-12.288	28.411	1.00	62.17	B
1848	CB	LEU	96	34.655	-12.602	28.027	1.00	58.63	B
1849	CG	LEU	96	35.459	-13.470	28.959	1.00	72.54	B
1850	CD1	LEU	96	36.860	-13.661	28.367	1.00	68.38	B
1851	CD2	LEU	96	35.464	-12.831	30.277	1.00	59.27	B
1852	C	LEU	96	32.836	-10.979	27.648	1.00	67.32	B
1853	O	LEU	96	32.445	-10.975	26.488	1.00	97.19	B
1854	N	THR	97	32.999	-9.871	28.326	1.00	93.07	B
1855	CA	THR	97	32.791	-8.564	27.728	1.00	45.15	B
1856	CB	THR	97	32.573	-7.590	28.865	1.00	46.72	B
1857	OG1	THR	97	31.200	-7.253	28.840	1.00	48.66	B
1858	CG2	THR	97	33.500	-6.395	28.860	1.00	57.90	B
1859	C	THR	97	34.070	-8.271	26.966	1.00	72.55	B
1860	O	THR	97	35.154	-8.777	27.351	1.00	66.92	B
1861	N	LEU	98	33.947	-7.478	25.893	1.00	70.04	B
1862	CA	LEU	98	35.084	-7.048	25.058	1.00	53.99	B
1863	CB	LEU	98	34.621	-6.092	23.975	1.00	84.69	B
1864	CG	LEU	98	34.634	-6.730	22.590	1.00	72.17	B
1865	CD1	LEU	98	36.034	-7.319	22.295	1.00	49.66	B
1866	CD2	LEU	98	33.631	-7.805	22.534	1.00	71.30	B
1867	C	LEU	98	36.052	-6.347	25.922	1.00	54.69	B
1868	O	LEU	98	37.258	-6.512	25.735	1.00	51.66	B
1869	N	GLY	99	35.515	-5.564	26.870	1.00	66.33	B

1870	CA	GLY	99	36.340	-4.845	27.814	1.00	59.00	B
1871	C	GLY	99	37.125	-5.819	28.662	1.00	79.84	B
1872	O	GLY	99	38.361	-5.799	28.650	1.00	67.38	B
1873	N	GLU	100	36.426	-6.673	29.405	1.00	62.74	B
1874	CA	GLU	100	37.121	-7.662	30.254	1.00	64.69	B
1875	CB	GLU	100	36.124	-8.661	30.796	1.00	54.20	B
1876	CG	GLU	100	34.974	-7.980	31.576	1.00	67.40	B
1877	CD	GLU	100	33.725	-8.855	31.744	1.00	91.60	B
1878	OE1	GLU	100	33.617	-9.929	31.085	1.00	99.71	B
1879	OE2	GLU	100	32.831	-8.438	32.536	1.00	94.44	B
1880	C	GLU	100	38.147	-8.407	29.417	1.00	78.41	B
1881	O	GLU	100	39.322	-8.523	29.794	1.00	93.92	B
1882	N	PHE	101	37.685	-8.914	28.282	1.00	47.91	B
1883	CA	PHE	101	38.585	-9.646	27.431	1.00	65.39	B
1884	CB	PHE	101	37.975	-10.063	26.080	1.00	44.63	B
1885	CG	PHE	101	38.978	-10.673	25.227	1.00	57.78	B
1886	CD1	PHE	101	39.668	-11.790	25.672	1.00	36.10	B
1887	CD2	PHE	101	39.414	-10.050	24.057	1.00	41.99	B
1888	CE1	PHE	101	40.819	-12.292	24.949	1.00	52.52	B
1889	CE2	PHE	101	40.547	-10.520	23.344	1.00	54.85	B
1890	CZ	PHE	101	41.248	-11.656	23.796	1.00	58.82	B
1891	C	PHE	101	39.816	-8.841	27.156	1.00	41.06	B
1892	O	PHE	101	40.943	-9.390	27.123	1.00	77.13	B
1893	N	LEU	102	39.666	-7.538	26.888	1.00	69.10	B
1894	CA	LEU	102	40.855	-6.688	26.638	1.00	82.85	B
1895	CB	LEU	102	40.410	-5.350	26.113	1.00	94.52	B
1896	CG	LEU	102	40.554	-5.210	24.597	1.00	91.94	B
1897	CD1	LEU	102	40.516	-6.529	23.897	1.00	63.98	B
1898	CD2	LEU	102	39.461	-4.276	24.115	1.00	59.88	B
1899	C	LEU	102	41.768	-6.489	27.877	1.00	62.86	B
1900	O	LEU	102	42.999	-6.398	27.803	1.00	56.85	B
1901	N	LYS	103	41.154	-6.388	29.035	1.00	48.66	B
1902	CA	LYS	103	41.874	-6.310	30.305	1.00	81.71	B
1903	CB	LYS	103	40.827	-6.199	31.420	1.00	78.64	B
1904	CG	LYS	103	41.353	-5.617	32.709	1.00	98.83	B
1905	CD	LYS	103	40.231	-5.406	33.703	1.00	116.71	B
1906	CE	LYS	103	40.750	-5.082	35.117	1.00	84.50	B
1907	NZ	LYS	103	39.584	-4.781	36.098	1.00	83.55	B
1908	C	LYS	103	42.739	-7.607	30.418	1.00	79.80	B
1909	O	LYS	103	43.964	-7.497	30.605	1.00	62.60	B
1910	N	LEU	104	42.139	-8.808	30.248	1.00	51.12	B
1911	CA	LEU	104	42.959	-10.050	30.335	1.00	45.92	B
1912	CB	LEU	104	42.125	-11.334	30.143	1.00	37.12	B
1913	CG	LEU	104	41.135	-11.392	31.319	1.00	49.35	B
1914	CD1	LEU	104	39.899	-12.120	30.942	1.00	45.00	B
1915	CD2	LEU	104	41.861	-12.008	32.527	1.00	72.74	B
1916	C	LEU	104	44.071	-10.074	29.371	1.00	45.78	B
1917	O	LEU	104	45.177	-10.589	29.670	1.00	61.79	B
1918	N	ASP	105	43.828	-9.502	28.198	1.00	61.78	B
1919	CA	ASP	105	44.894	-9.560	27.207	1.00	44.57	B
1920	CB	ASP	105	44.334	-9.356	25.787	1.00	73.64	B

1921	CG	ASP	105	45.084	-10.198	24.751	1.00	61.01	B
1922	OD1	ASP	105	46.357	-10.245	24.786	1.00	72.36	B
1923	OD2	ASP	105	44.446	-10.861	23.904	1.00	132.49	B
1924	C	ASP	105	45.948	-8.574	27.560	1.00	35.76	B
1925	O	ASP	105	47.205	-8.742	27.269	1.00	44.36	B
1926	N	ARG	106	45.496	-7.540	28.263	1.00	63.38	B
1927	CA	ARG	106	46.470	-6.551	28.637	1.00	67.59	B
1928	CB	ARG	106	45.779	-5.272	29.099	1.00	79.25	B
1929	CG	ARG	106	46.040	-4.111	28.129	1.00	62.28	B
1930	CD	ARG	106	45.175	-2.872	28.449	1.00	46.47	B
1931	NE	ARG	106	43.900	-3.181	29.061	1.00	47.23	B
1932	CZ	ARG	106	42.756	-2.543	28.833	1.00	45.33	B
1933	NH1	ARG	106	42.730	-1.531	27.966	1.00	135.43	B
1934	NH2	ARG	106	41.597	-2.870	29.487	1.00	58.26	B
1935	C	ARG	106	47.342	-7.207	29.705	1.00	60.30	B
1936	O	ARG	106	48.550	-7.126	29.623	1.00	58.02	B
1937	N	GLU	107	46.740	-7.924	30.658	1.00	54.67	B
1938	CA	GLU	107	47.518	-8.631	31.707	1.00	63.96	B
1939	CB	GLU	107	46.589	-9.273	32.712	1.00	56.27	B
1940	CG	GLU	107	47.309	-9.900	33.902	1.00	69.85	B
1941	CD	GLU	107	46.301	-10.229	35.021	1.00	68.32	B
1942	OE1	GLU	107	46.692	-10.842	36.073	1.00	95.89	B
1943	OE2	GLU	107	45.105	-9.858	34.802	1.00	76.01	B
1944	C	GLU	107	48.359	-9.722	31.088	1.00	76.16	B
1945	O	GLU	107	49.533	-9.898	31.445	1.00	70.88	B
1946	N	ARG	108	47.770	-10.472	30.153	1.00	74.73	B
1947	CA	ARG	108	48.582	-11.530	29.558	1.00	64.97	B
1948	CB	ARG	108	47.837	-12.336	28.459	1.00	82.38	B
1949	CG	ARG	108	48.799	-13.222	27.544	1.00	49.97	B
1950	CD	ARG	108	48.107	-14.407	27.006	1.00	66.81	B
1951	NE	ARG	108	47.081	-14.060	26.011	1.00	93.64	B
1952	CZ	ARG	108	47.327	-13.885	24.707	1.00	75.36	B
1953	NH1	ARG	108	48.529	-14.012	24.231	1.00	54.84	B
1954	NH2	ARG	108	46.387	-13.604	23.847	1.00	64.28	B
1955	C	ARG	108	49.863	-10.963	28.986	1.00	59.85	B
1956	O	ARG	108	50.981	-11.482	29.252	1.00	75.91	B
1957	N	ALA	109	49.763	-9.901	28.184	1.00	74.96	B
1958	CA	ALA	109	51.026	-9.421	27.596	1.00	83.83	B
1959	CB	ALA	109	50.767	-8.333	26.546	1.00	95.75	B
1960	C	ALA	109	52.020	-8.946	28.691	1.00	86.26	B
1961	O	ALA	109	53.231	-9.060	28.510	1.00	68.54	B
1962	N	LYS	110	51.505	-8.438	29.820	1.00	65.94	B
1963	CA	LYS	110	52.309	-7.999	30.965	1.00	78.67	B
1964	CB	LYS	110	51.363	-7.520	32.059	1.00	92.51	B
1965	CG	LYS	110	51.970	-6.632	33.128	1.00	114.74	B
1966	CD	LYS	110	50.899	-6.239	34.171	1.00	128.43	B
1967	CE	LYS	110	51.533	-5.693	35.468	1.00	124.19	B
1968	NZ	LYS	110	50.563	-5.261	36.535	1.00	105.96	B
1969	C	LYS	110	53.114	-9.231	31.435	1.00	84.58	B
1970	O	LYS	110	54.347	-9.260	31.331	1.00	67.62	B
1971	N	ASN	111	52.431	-10.245	31.949	1.00	65.21	B

1972	CA	ASN	111	53.139	-11.478	32.317	1.00	57.99	B
1973	CB	ASN	111	52.125	-12.613	32.485	1.00	31.04	B
1974	CG	ASN	111	50.982	-12.227	33.387	1.00	54.19	B
1975	OD1	ASN	111	51.043	-11.241	34.104	1.00	89.00	B
1976	ND2	ASN	111	49.921	-13.030	33.372	1.00	57.24	B
1977	C	ASN	111	54.199	-11.937	31.281	1.00	47.21	B
1978	O	ASN	111	55.279	-12.406	31.631	1.00	94.10	B
1979	N	LYS	112	53.889	-11.796	29.997	1.00	79.09	B
1980	CA	LYS	112	54.867	-12.257	29.017	1.00	89.00	B
1981	CB	LYS	112	54.307	-12.196	27.586	1.00	77.60	B
1982	CG	LYS	112	55.234	-12.826	26.546	1.00	67.02	B
1983	CD	LYS	112	54.722	-12.713	25.116	1.00	87.37	B
1984	CE	LYS	112	55.874	-12.920	24.120	1.00	106.22	B
1985	NZ	LYS	112	55.749	-12.290	22.749	1.00	106.45	B
1986	C	LYS	112	56.128	-11.432	29.149	1.00	75.06	B
1987	O	LYS	112	57.227	-11.968	28.963	1.00	82.99	B
1988	N	ILE	113	55.963	-10.133	29.443	1.00	87.97	B
1989	CA	ILE	113	57.070	-9.171	29.632	1.00	85.00	B
1990	CB	ILE	113	56.521	-7.753	29.839	1.00	80.58	B
1991	CG2	ILE	113	57.407	-6.929	30.703	1.00	69.74	B
1992	CG1	ILE	113	56.403	-7.114	28.488	1.00	83.83	B
1993	CD1	ILE	113	57.686	-7.228	27.762	1.00	87.93	B
1994	C	ILE	113	57.832	-9.604	30.857	1.00	88.70	B
1995	O	ILE	113	59.026	-9.922	30.797	1.00	79.43	B
1996	N	ALA	114	57.097	-9.640	31.966	1.00	75.23	B
1997	CA	ALA	114	57.600	-10.092	33.260	1.00	68.38	B
1998	CB	ALA	114	56.415	-10.460	34.150	1.00	53.36	B
1999	C	ALA	114	58.486	-11.316	32.991	1.00	87.61	B
2000	O	ALA	114	59.697	-11.289	33.270	1.00	92.76	B
2001	N	LYS	115	57.903	-12.374	32.407	1.00	71.60	B
2002	CA	LYS	115	58.677	-13.567	32.112	1.00	54.50	B
2003	CB	LYS	115	57.806	-14.718	31.541	1.00	78.75	B
2004	CG	LYS	115	58.631	-15.983	31.224	1.00	72.89	B
2005	CD	LYS	115	57.762	-17.204	31.237	1.00	107.71	B
2006	CE	LYS	115	58.543	-18.463	30.922	1.00	90.87	B
2007	NZ	LYS	115	57.591	-19.589	30.591	1.00	103.11	B
2008	C	LYS	115	59.924	-13.406	31.261	1.00	46.41	B
2009	O	LYS	115	60.942	-14.095	31.507	1.00	84.50	B
2010	N	GLU	116	59.927	-12.530	30.268	1.00	72.57	B
2011	CA	GLU	116	61.176	-12.431	29.486	1.00	75.74	B
2012	CB	GLU	116	60.893	-11.834	28.103	1.00	120.58	B
2013	CG	GLU	116	60.193	-10.490	28.203	1.00	141.76	B
2014	CD	GLU	116	60.488	-9.533	27.039	1.00	147.04	B
2015	OE1	GLU	116	61.681	-9.292	26.668	1.00	126.42	B
2016	OE2	GLU	116	59.497	-8.990	26.503	1.00	133.70	B
2017	C	GLU	116	62.202	-11.563	30.265	1.00	87.76	B
2018	O	GLU	116	63.404	-11.701	30.069	1.00	81.99	B
2019	N	THR	117	61.722	-10.681	31.146	1.00	77.42	B
2020	CA	THR	117	62.582	-9.813	31.951	1.00	87.65	B
2021	CB	THR	117	61.750	-8.902	32.830	1.00	87.12	B
2022	OG1	THR	117	60.884	-8.146	32.006	1.00	90.52	B

2023	CG2	THR	117	62.608	-7.986	33.651	1.00	108.15	B
2024	C	THR	117	63.346	-10.732	32.885	1.00	94.05	B
2025	O	THR	117	64.565	-10.630	33.010	1.00	81.93	B
2026	N	ASN	118	62.606	-11.626	33.547	1.00	79.30	B
2027	CA	ASN	118	63.206	-12.578	34.471	1.00	55.15	B
2028	CB	ASN	118	62.155	-13.441	35.083	1.00	70.64	B
2029	CG	ASN	118	62.381	-13.631	36.545	1.00	99.94	B
2030	OD1	ASN	118	63.435	-14.099	36.969	1.00	97.11	B
2031	ND2	ASN	118	61.400	-13.255	37.335	1.00	112.94	B
2032	C	ASN	118	64.253	-13.402	33.766	1.00	69.17	B
2033	O	ASN	118	65.342	-13.636	34.293	1.00	87.42	B
2034	N	ASN	119	63.970	-13.782	32.529	1.00	69.56	B
2035	CA	ASN	119	64.971	-14.545	31.796	1.00	56.83	B
2036	CB	ASN	119	64.503	-14.980	30.400	1.00	110.50	B
2037	CG	ASN	119	63.173	-15.649	30.421	1.00	106.31	B
2038	OD1	ASN	119	62.874	-16.412	31.347	1.00	82.76	B
2039	ND2	ASN	119	62.344	-15.362	29.406	1.00	118.40	B
2040	C	ASN	119	66.215	-13.788	31.609	1.00	60.40	B
2041	O	ASN	119	67.325	-14.338	31.853	1.00	69.22	B
2042	N	LYS	120	66.056	-12.541	31.136	1.00	78.27	B
2043	CA	LYS	120	67.206	-11.678	30.906	1.00	84.44	B
2044	CB	LYS	120	66.802	-10.297	30.368	1.00	89.48	B
2045	CG	LYS	120	66.580	-10.226	28.847	1.00	93.05	B
2046	CD	LYS	120	65.574	-9.102	28.497	1.00	95.97	B
2047	CE	LYS	120	65.264	-8.962	27.019	1.00	67.82	B
2048	NZ	LYS	120	66.529	-8.616	26.224	1.00	100.51	B
2049	C	LYS	120	67.983	-11.535	32.223	1.00	51.04	B
2050	O	LYS	120	69.213	-11.554	32.145	1.00	47.24	B
2051	N	LYS	121	67.326	-11.451	33.412	1.00	48.93	B
2052	CA	LYS	121	68.115	-11.322	34.660	1.00	47.10	B
2053	CB	LYS	121	67.221	-11.148	35.913	1.00	82.19	B
2054	CG	LYS	121	66.830	-9.693	36.151	1.00	115.71	B
2055	CD	LYS	121	65.559	-9.490	36.996	1.00	134.54	B
2056	CE	LYS	121	64.924	-8.095	36.700	1.00	131.39	B
2057	NZ	LYS	121	63.694	-7.737	37.502	1.00	123.69	B
2058	C	LYS	121	69.008	-12.561	34.845	1.00	75.10	B
2059	O	LYS	121	70.243	-12.454	35.044	1.00	52.11	B
2060	N	LYS	122	68.383	-13.740	34.785	1.00	52.65	B
2061	CA	LYS	122	69.130	-15.002	34.938	1.00	59.46	B
2062	CB	LYS	122	68.187	-16.185	34.756	1.00	70.96	B
2063	CG	LYS	122	67.037	-16.127	35.734	1.00	82.86	B
2064	CD	LYS	122	66.054	-17.316	35.627	1.00	94.74	B
2065	CE	LYS	122	64.998	-17.228	36.778	1.00	102.34	B
2066	NZ	LYS	122	64.175	-18.461	36.845	1.00	94.19	B
2067	C	LYS	122	70.262	-15.063	33.930	1.00	72.45	B
2068	O	LYS	122	71.419	-15.355	34.274	1.00	89.33	B
2069	N	GLU	123	69.955	-14.759	32.678	1.00	63.90	B
2070	CA	GLU	123	71.019	-14.776	31.666	1.00	78.09	B
2071	CB	GLU	123	70.393	-14.543	30.277	1.00	99.36	B
2072	CG	GLU	123	69.604	-15.732	29.740	1.00	126.86	B
2073	CD	GLU	123	68.531	-15.336	28.735	1.00	145.43	B

2074	OE1	GLU	123	68.868	-14.662	27.739	1.00	150.58	B
2075	OE2	GLU	123	67.349	-15.711	28.933	1.00	142.15	B
2076	C	GLU	123	72.151	-13.744	31.978	1.00	76.57	B
2077	O	GLU	123	73.363	-14.024	31.805	1.00	68.73	B
2078	N	PHE	124	71.766	-12.554	32.448	1.00	67.99	B
2079	CA	PHE	124	72.748	-11.554	32.800	1.00	64.15	B
2080	CB	PHE	124	72.062	-10.235	33.182	1.00	91.07	B
2081	CG	PHE	124	73.005	-9.096	33.330	1.00	89.42	B
2082	CD1	PHE	124	73.785	-8.705	32.251	1.00	80.16	B
2083	CD2	PHE	124	73.219	-8.505	34.577	1.00	95.90	B
2084	CE1	PHE	124	74.800	-7.746	32.390	1.00	51.10	B
2085	CE2	PHE	124	74.232	-7.538	34.741	1.00	100.31	B
2086	CZ	PHE	124	75.031	-7.165	33.628	1.00	102.36	B
2087	C	PHE	124	73.581	-12.076	33.974	1.00	94.37	B
2088	O	PHE	124	74.793	-12.145	33.834	1.00	45.14	B
2089	N	GLU	125	72.970	-12.493	35.102	1.00	34.38	B
2090	CA	GLU	125	73.739	-12.973	36.284	1.00	90.41	B
2091	CB	GLU	125	72.796	-13.341	37.426	1.00	49.81	B
2092	CG	GLU	125	71.890	-12.146	37.711	1.00	106.32	B
2093	CD	GLU	125	70.816	-12.418	38.746	1.00	142.97	B
2094	OE1	GLU	125	70.001	-13.355	38.525	1.00	129.71	B
2095	OE2	GLU	125	70.787	-11.680	39.769	1.00	157.45	B
2096	C	GLU	125	74.694	-14.093	35.977	1.00	59.41	B
2097	O	GLU	125	75.811	-14.116	36.477	1.00	85.90	B
2098	N	GLU	126	74.267	-14.999	35.107	1.00	70.75	B
2099	CA	GLU	126	75.132	-16.092	34.680	1.00	58.88	B
2100	CB	GLU	126	74.476	-16.931	33.592	1.00	112.77	B
2101	CG	GLU	126	74.135	-18.362	33.970	1.00	139.37	B
2102	CD	GLU	126	73.910	-19.254	32.741	1.00	141.26	B
2103	OE1	GLU	126	73.331	-20.343	32.898	1.00	146.37	B
2104	OE2	GLU	126	74.320	-18.885	31.617	1.00	135.49	B
2105	C	GLU	126	76.393	-15.559	34.102	1.00	62.08	B
2106	O	GLU	126	77.489	-16.039	34.394	1.00	96.24	B
2107	N	THR	127	76.243	-14.595	33.206	1.00	75.42	B
2108	CA	THR	127	77.394	-13.999	32.561	1.00	72.75	B
2109	CB	THR	127	76.920	-13.041	31.533	1.00	80.30	B
2110	OG1	THR	127	75.844	-13.685	30.856	1.00	84.42	B
2111	CG2	THR	127	78.084	-12.586	30.567	1.00	51.20	B
2112	C	THR	127	78.230	-13.254	33.571	1.00	67.63	B
2113	O	THR	127	79.454	-13.324	33.534	1.00	57.32	B
2114	N	ALA	128	77.566	-12.524	34.458	1.00	71.09	B
2115	CA	ALA	128	78.257	-11.778	35.497	1.00	75.61	B
2116	CB	ALA	128	77.258	-11.204	36.454	1.00	63.68	B
2117	C	ALA	128	79.222	-12.745	36.205	1.00	91.61	B
2118	O	ALA	128	80.436	-12.423	36.265	1.00	70.17	B
2119	N	LYS	129	78.717	-13.918	36.676	1.00	63.90	B
2120	CA	LYS	129	79.569	-14.946	37.362	1.00	71.28	B
2121	CB	LYS	129	78.813	-16.218	37.764	1.00	73.07	B
2122	CG	LYS	129	77.838	-16.095	38.940	1.00	88.83	B
2123	CD	LYS	129	77.461	-17.486	39.462	1.00	104.12	B
2124	CE	LYS	129	76.362	-17.472	40.558	1.00	111.10	B

2125	NZ	LYS	129	76.013	-18.841	41.135	1.00	98.35	B
2126	C	LYS	129	80.710	-15.428	36.496	1.00	58.99	B
2127	O	LYS	129	81.840	-15.560	36.950	1.00	71.83	B
2128	N	LYS	130	80.441	-15.715	35.237	1.00	70.97	B
2129	CA	LYS	130	81.539	-16.190	34.405	1.00	63.37	B
2130	CB	LYS	130	81.025	-16.637	33.005	1.00	84.15	B
2131	CG	LYS	130	79.868	-17.685	33.010	1.00	103.16	B
2132	CD	LYS	130	79.731	-18.528	31.698	1.00	99.81	B
2133	CE	LYS	130	79.216	-17.733	30.499	1.00	119.36	B
2134	NZ	LYS	130	79.226	-18.502	29.212	1.00	104.79	B
2135	C	LYS	130	82.602	-15.086	34.305	1.00	66.85	B
2136	O	LYS	130	83.819	-15.339	34.398	1.00	76.85	B
2137	N	VAL	131	82.165	-13.838	34.138	1.00	72.72	B
2138	CA	VAL	131	83.107	-12.751	34.023	1.00	64.47	B
2139	CB	VAL	131	82.398	-11.475	33.540	1.00	77.19	B
2140	CG1	VAL	131	83.337	-10.196	33.633	1.00	57.95	B
2141	CG2	VAL	131	81.998	-11.691	32.126	1.00	67.68	B
2142	C	VAL	131	83.868	-12.510	35.320	1.00	74.88	B
2143	O	VAL	131	85.078	-12.465	35.286	1.00	46.20	B
2144	N	ARG	132	83.185	-12.327	36.445	1.00	47.61	B
2145	CA	ARG	132	83.843	-12.132	37.758	1.00	98.93	B
2146	CB	ARG	132	82.820	-12.214	38.853	1.00	88.72	B
2147	CG	ARG	132	83.384	-11.769	40.108	1.00	75.39	B
2148	CD	ARG	132	82.327	-11.845	41.172	1.00	79.86	B
2149	NE	ARG	132	81.086	-11.350	40.595	1.00	115.19	B
2150	CZ	ARG	132	80.110	-10.766	41.284	1.00	131.24	B
2151	NH1	ARG	132	80.223	-10.601	42.610	1.00	134.31	B
2152	NH2	ARG	132	79.033	-10.323	40.629	1.00	115.31	B
2153	C	ARG	132	84.929	-13.166	38.080	1.00	84.43	B
2154	O	ARG	132	86.093	-12.831	38.416	1.00	71.53	B
2155	N	ARG	133	84.510	-14.418	37.991	1.00	66.66	B
2156	CA	ARG	133	85.372	-15.554	38.242	1.00	70.19	B
2157	CB	ARG	133	84.672	-16.892	37.876	1.00	77.91	B
2158	CG	ARG	133	85.569	-17.910	37.109	1.00	128.58	B
2159	CD	ARG	133	84.798	-19.044	36.341	1.00	160.56	B
2160	NE	ARG	133	85.652	-19.753	35.360	1.00	166.68	B
2161	CZ	ARG	133	85.361	-20.921	34.774	1.00	156.25	B
2162	NH1	ARG	133	84.224	-21.552	35.053	1.00	142.35	B
2163	NH2	ARG	133	86.219	-21.471	33.911	1.00	133.54	B
2164	C	ARG	133	86.614	-15.432	37.412	1.00	61.37	B
2165	O	ARG	133	87.755	-15.495	37.919	1.00	92.09	B
2166	N	ALA	134	86.404	-15.252	36.127	1.00	70.56	B
2167	CA	ALA	134	87.534	-15.214	35.234	1.00	73.24	B
2168	CB	ALA	134	87.063	-15.082	33.866	1.00	61.64	B
2169	C	ALA	134	88.514	-14.123	35.529	1.00	83.63	B
2170	O	ALA	134	89.713	-14.275	35.275	1.00	80.73	B
2171	N	ILE	135	87.996	-13.010	36.046	1.00	92.66	B
2172	CA	ILE	135	88.800	-11.842	36.359	1.00	88.85	B
2173	CB	ILE	135	87.913	-10.624	36.397	1.00	94.11	B
2174	CG2	ILE	135	87.504	-10.265	37.815	1.00	102.99	B
2175	CG1	ILE	135	88.629	-9.508	35.687	1.00	94.00	B

2176	CD1	ILE	135	87.708	-8.836	34.752	1.00	67.18	B
2177	C	ILE	135	89.515	-12.058	37.681	1.00	104.59	B
2178	O	ILE	135	90.717	-11.706	37.821	1.00	76.80	B
2179	N	GLU	136	88.768	-12.627	38.639	1.00	100.63	B
2180	CA	GLU	136	89.329	-13.003	39.934	1.00	55.99	B
2181	CB	GLU	136	88.311	-13.812	40.724	1.00	72.57	B
2182	CG	GLU	136	87.412	-12.918	41.629	1.00	76.04	B
2183	CD	GLU	136	86.247	-13.691	42.269	1.00	115.29	B
2184	OE1	GLU	136	86.377	-14.951	42.384	1.00	117.79	B
2185	OE2	GLU	136	85.229	-13.022	42.660	1.00	77.42	B
2186	C	GLU	136	90.570	-13.854	39.617	1.00	87.38	B
2187	O	GLU	136	91.702	-13.453	39.924	1.00	108.79	B
2188	N	GLN	137	90.370	-15.005	38.979	1.00	78.79	B
2189	CA	GLN	137	91.520	-15.841	38.577	1.00	77.42	B
2190	CB	GLN	137	91.084	-16.895	37.579	1.00	88.86	B
2191	CG	GLN	137	90.084	-17.854	38.132	1.00	92.37	B
2192	CD	GLN	137	89.623	-18.794	37.073	1.00	108.07	B
2193	OE1	GLN	137	90.384	-19.111	36.136	1.00	99.63	B
2194	NE2	GLN	137	88.372	-19.259	37.197	1.00	108.75	B
2195	C	GLN	137	92.717	-15.131	37.977	1.00	80.77	B
2196	O	GLN	137	93.860	-15.662	37.959	1.00	87.84	B
2197	N	LEU	138	92.480	-13.950	37.430	1.00	88.29	B
2198	CA	LEU	138	93.577	-13.217	36.827	1.00	92.29	B
2199	CB	LEU	138	93.038	-12.187	35.831	1.00	63.24	B
2200	CG	LEU	138	94.029	-11.220	35.221	1.00	65.59	B
2201	CD1	LEU	138	95.191	-11.985	34.548	1.00	65.60	B
2202	CD2	LEU	138	93.323	-10.399	34.192	1.00	94.60	B
2203	C	LEU	138	94.348	-12.545	37.960	1.00	80.74	B
2204	O	LEU	138	95.552	-12.379	37.868	1.00	75.19	B
2205	N	ALA	139	93.668	-12.167	39.039	1.00	95.90	B
2206	CA	ALA	139	94.339	-11.543	40.192	1.00	108.82	B
2207	CB	ALA	139	93.334	-10.650	40.931	1.00	72.14	B
2208	C	ALA	139	94.819	-12.712	41.092	1.00	109.76	B
2209	O	ALA	139	94.300	-12.923	42.195	1.00	112.51	B
2210	N	ALA	140	95.797	-13.472	40.578	1.00	131.24	B
2211	CA	ALA	140	96.369	-14.686	41.205	1.00	127.02	B
2212	CB	ALA	140	95.265	-15.790	41.429	1.00	62.56	B
2213	C	ALA	140	97.465	-15.255	40.287	1.00	116.80	B
2214	O	ALA	140	98.406	-15.916	40.806	1.00	134.41	B
2215	OXT	ALA	140	97.348	-15.055	39.045	1.00	78.60	B
2216	ZN+2	ZN2	341	24.738	.656	7.998	1.00	82.63	
2217	ZN+2	ZN2	342	48.200	-19.195	34.618	1.00	79.52	
2218	S	SO4	500	24.499	-16.774	13.690	1.00	148.83	
2219	O1	SO4	500	24.445	-17.606	12.492	1.00	132.99	
2220	O2	SO4	500	23.919	-15.475	13.459	1.00	112.17	
2221	O3	SO4	500	25.897	-16.500	13.883	1.00	109.73	
2222	O4	SO4	500	23.900	-17.357	14.907	1.00	142.05	
2223	S	SO4	501	24.192	1.125	-2.858	1.00	156.84	
2224	O1	SO4	501	25.428	1.050	-3.711	1.00	121.87	

2225	O2	SO4	501	23.073	.310	-3.400	1.00	131.46	
2226	O3	SO4	501	23.738	2.538	-2.740	1.00	133.77	
2227	O4	SO4	501	24.511	.601	-1.522	1.00	144.15	
2228	S	SO4	502	43.786	-2.153	32.837	1.00	141.64	
2229	O1	SO4	502	44.157	-2.834	34.107	1.00	154.38	
2230	O2	SO4	502	44.966	-2.085	31.927	1.00	103.98	
2231	O3	SO4	502	43.269	-.784	33.070	1.00	137.77	
2232	O4	SO4	502	42.696	-2.926	32.231	1.00	153.82	
2233	OH2	WAT	1000	32.411	2.511	20.110	1.00	69.51	
2234	OH2	WAT	1001	31.260	-.677	17.246	1.00	55.37	
2235	OH2	WAT	1002	24.550	-12.184	-8.601	1.00	54.86	
2236	OH2	WAT	1003	32.665	4.454	1.761	1.00	86.91	
2237	OH2	WAT	1004	39.065	-17.756	28.187	1.00	52.36	
2238	OH2	WAT	1005	34.723	-10.054	5.120	1.00	68.46	
2239	OH2	WAT	1006	25.098	-12.623	-2.377	1.00	51.68	
2240	OH2	WAT	1007	23.182	-6.307	8.560	1.00	48.99	
2241	OH2	WAT	1008	25.900	10.393	13.891	1.00	57.98	
2242	OH2	WAT	1009	28.223	-4.653	29.091	1.00	87.74	
2243	OH2	WAT	1010	40.338	-40.512	30.423	1.00	80.40	
2244	OH2	WAT	1011	19.555	-5.962	-11.102	1.00	74.26	
2245	OH2	WAT	1012	38.566	-19.321	16.326	1.00	81.47	
2246	OH2	WAT	1013	33.530	15.644	13.569	1.00	79.81	
2247	OH2	WAT	1014	32.787	-19.954	24.409	1.00	61.58	
2248	OH2	WAT	1015	33.604	-2.871	6.961	1.00	59.94	
2249	OH2	WAT	1016	48.549	-10.785	25.080	1.00	54.98	
2250	OH2	WAT	1017	26.358	1.775	17.521	1.00	89.68	
2251	OH2	WAT	1018	48.149	-13.182	35.456	1.00	60.07	
2252	OH2	WAT	1019	19.725	-2.316	-23.486	1.00	75.81	
2253	OH2	WAT	1020	59.020	-7.243	33.899	1.00	73.29	
2254	OH2	WAT	1021	44.807	14.435	5.807	1.00	86.53	
2255	OH2	WAT	1022	25.114	21.706	11.042	1.00	93.94	
2256	OH2	WAT	1023	21.239	-12.563	-5.724	1.00	59.14	
2257	OH2	WAT	1024	40.659	-1.204	21.417	1.00	68.35	
2258	OH2	WAT	1025	18.054	10.968	.705	1.00	60.82	
2259	OH2	WAT	1026	19.410	11.418	9.365	1.00	61.98	
2260	OH2	WAT	1027	24.595	2.691	22.024	1.00	98.75	
2261	OH2	WAT	1028	51.015	-10.947	24.696	1.00	69.67	
2262	OH2	WAT	1029	38.722	-.337	22.509	1.00	63.85	
2263	OH2	WAT	1030	23.073	-8.689	-24.392	1.00	63.92	
2264	OH2	WAT	1031	24.035	19.739	-1.118	1.00	83.78	
2265	OH2	WAT	1032	57.211	-27.525	31.393	1.00	85.92	
2266	OH2	WAT	1033	33.069	-9.466	9.036	1.00	55.47	
2267	OH2	WAT	1034	36.857	-21.441	25.913	1.00	66.23	
2268	OH2	WAT	1035	38.755	-13.006	37.840	1.00	79.37	
2269	OH2	WAT	1036	20.838	-12.643	-.796	1.00	65.80	
2270	OH2	WAT	1037	64.699	-38.597	23.370	1.00	90.06	
2271	OH2	WAT	1038	22.891	11.579	1.474	1.00	59.37	
2272	OH2	WAT	1039	40.241	-18.768	11.867	1.00	71.52	
2273	OH2	WAT	1040	42.195	-38.365	24.878	1.00	93.43	
2274	OH2	WAT	1041	40.228	9.327	17.145	1.00	70.00	
2275	OH2	WAT	1042	24.824	12.442	-5.046	1.00	81.13	

2276	OH2	WAT	1043	22.833	-10.979	-20.805	1.00	62.01	
2277	OH2	WAT	1044	29.350	2.084	-34.168	1.00	74.41	
2278	OH2	WAT	1045	24.706	-9.746	18.777	1.00	59.87	
2279	OH2	WAT	1046	40.841	-13.007	36.362	1.00	85.99	
2280	OH2	WAT	1047	40.039	12.160	-4.002	1.00	87.18	
2281	OH2	WAT	1048	96.766	-16.715	37.077	1.00	64.89	
2282	OH2	WAT	1049	37.380	-20.948	32.143	1.00	79.88	
2283	OH2	WAT	1050	33.342	2.295	18.022	1.00	80.97	
2284	OH2	WAT	1051	35.079	-22.502	26.806	1.00	81.60	
2285	OH2	WAT	1052	35.025	6.061	20.571	1.00	67.51	
2286	OH2	WAT	1053	20.312	21.645	-2.090	1.00	85.53	
2287	OH2	WAT	1054	33.487	-6.399	-5.811	1.00	80.99	
2288	OH2	WAT	1055	26.268	-14.260	20.169	1.00	85.72	
2289	OH2	WAT	1056	40.057	-1.464	26.753	1.00	86.45	
2290	OH2	WAT	1057	34.593	23.946	7.685	1.00	46.16	
2291	OH2	WAT	1058	17.726	-6.721	11.638	1.00	90.37	
2292	OH2	WAT	1059	39.074	-21.322	27.899	1.00	53.98	
2293	OH2	WAT	1060	34.077	1.155	23.598	1.00	65.84	
2294	OH2	WAT	1061	41.168	-26.408	45.257	1.00	95.99	
2295	OH2	WAT	1062	36.398	11.612	18.598	1.00	94.64	
2296	OH2	WAT	1063	29.043	1.338	18.535	1.00	75.76	
2297	OH2	WAT	1064	26.205	15.164	-5.742	1.00	75.21	
2298	OH2	WAT	1065	18.802	-9.311	-21.172	1.00	76.64	
2299	OH2	WAT	1066	39.882	-12.277	41.271	1.00	66.04	
2300	OH2	WAT	1067	34.154	23.208	2.107	1.00	52.83	
2301	OH2	WAT	1068	62.103	-30.533	18.312	1.00	84.40	
2302	OH2	WAT	1069	17.557	-.586	-19.937	1.00	92.84	
2303	OH2	WAT	1070	38.265	-17.981	13.126	1.00	76.37	
2304	OH2	WAT	1071	36.881	2.698	26.720	1.00	69.37	
2305	OH2	WAT	1072	26.236	-1.040	-7.386	1.00	70.29	
2306	OH2	WAT	1073	35.217	2.987	20.117	1.00	77.70	
2307	OH2	WAT	1074	53.064	-10.920	22.341	1.00	70.81	
2308	OH2	WAT	1075	34.122	-13.204	-11.617	1.00	77.21	
2309	OH2	WAT	1076	49.179	-16.621	24.681	1.00	96.06	
2310	OH2	WAT	1077	53.510	-19.801	24.796	1.00	73.33	
2311	OH2	WAT	1078	37.031	-15.693	11.403	1.00	94.32	
2312	OH2	WAT	1079	52.436	-14.012	35.697	1.00	64.41	
2313	OH2	WAT	1080	56.272	-6.929	33.711	1.00	71.46	
2314	OH2	WAT	1081	34.636	-28.230	19.554	1.00	92.36	
2315	OH2	WAT	1082	99.849	-14.670	38.793	1.00	77.46	
2316	OH2	WAT	1083	41.112	-18.754	15.599	1.00	80.28	
2317	OH2	WAT	1084	32.532	-11.442	3.568	1.00	51.91	
2318	OH2	WAT	1085	43.660	24.253	6.975	1.00	79.62	
2319	OH2	WAT	1086	34.426	-19.011	19.976	1.00	63.01	
2320	OH2	WAT	1087	36.950	-13.626	35.104	1.00	77:12	
2321	OH2	WAT	1088	34.549	-14.707	35.862	1.00	79.20	
2322	OH2	WAT	1089	23.875	-13.550	11.621	1.00	52.66	

In addition, in accordance with this invention, an IAP or survivin polypeptide mutant may be crystallized in association or complex with known IAP binding agents, substrates, or inhibitors. The crystal structures of a series of such complexes may then be solved by molecular replacement and compared with that of a wild-type IAP molecule. Potential sites for modification within the IAP molecule may thus be identified. This information provides an additional tool for determining the most efficient binding interactions, for example, increased hydrophobic interactions, between an IAP and a chemical entity or compound.

All of the complexes referred to above may be studied using well-known X-ray diffraction techniques and may be refined versus 2-3 Å resolution X-ray data to an R value of about 0.20 or less using computer software, such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.). See, *e.g.*, Blundel & Johnson, *supra;* Methods in Enzymology, vol. 114 and 115, H. W. Wyckoff *et al.*, eds., Academic Press (1985). This information may thus be used to optimize known classes of IAP binding agents or substrates (*e.g.*, inhibitors), and to design and synthesize novel classes of IAP binding agents (*e.g.*, inhibitors).

The design of compounds or binding agents that bind to or inhibit an IAP polypeptide according to the invention generally involves consideration of two factors. First, the compound or binding agent must be capable of physically and structurally associating with an IAP molecule. Non-covalent molecular interactions important in the association of an IAP with a substrate include hydrogen bonding, van der Waals and hydrophobic interactions, and the like.

Second, the compound or binding agent must be able to assume a conformation that allows it to associate with an IAP molecule. Although certain portions of the compound or binding agent will not directly participate in this association, those portions may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical entity or compound in relation to all or a portion of the binding site, *e.g.*, active site or accessory binding site of an IAP polypeptide (*e.g.*, a survivin polypeptide), or the spacing between functional

groups of a compound comprising several chemical entities that directly interact with an IAP.

The potential inhibitory or binding effect of a chemical compound on an IAP may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and an IAP, synthesis and testing of the compound may be obviated. However, if computer modeling indicates a strong interaction, the molecule may then be tested for its ability to bind to an IAP. Methods of assaying for IAP activity are known in the art (as identified and discussed herein). Methods for assaying the effect of a potential binding agent can be performed in the presence of a known binding agent of an IAP. For example, the effect of the potential binding agent can be assayed by measuring the ability of the potential binding agent to compete with a known binding agent.

An inhibitory or other binding compound of an IAP may be computationally evaluated and designed by means of a series of steps in which chemical entities or fragments are screened and selected for their ability to associate with the individual binding pockets or other areas of an IAP.

One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with an IAP and more particularly with the individual binding pockets of a survivin polypeptide. This process may begin by visual inspection of, for example, the active site on the computer screen based on the survivin coordinates in Table 1. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within an individual binding pocket of an IAP. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics forcefields, such as CHARMM and AMBER.

Specialized computer programs may also assist in the process of selecting fragments or chemical entities. These include:

1. GRID (Goodford, P. J., "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J.

Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

2. MCSS (Miranker, A. and M. Karplus, "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure. Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, Mass.

3. AUTODOCK (Goodsell, D. S. and A. J. Olsen, "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure. Function, and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from Scripps Research Institute, La Jolla, Calif.

4. DOCK (Kuntz, I. D. *et al.*, "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from University of California, San Francisco, Calif.

Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or binding agent (*e.g.*, an inhibitor). Assembly may be performed by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of the survivin molecule as set forth in Table 1. This would be followed by manual model building using software such as Quanta or Sybyl.

Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include:

1. CAVEAT (Bartlett, P. A. et al, "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules". In "Molecular Recognition in Chemical and Biological Problems", Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, Calif.

2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif.). This area is reviewed in Martin, Y. C., "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992)).

3. HOOK (available from Molecular Simulations, Burlington, Mass.).

In addition to the method of building or identifying an IAP binding agent in a step-wise fashion one fragment or chemical entity at a time as described above, inhibitory or other IAP interaction compounds may be designed as a whole or "de novo" using either an empty active site or optionally including some portion(s) of a known inhibitor(s). These methods include:

1. LUDI (Bohm, H.-J., "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", J. Comp. Aid. Molec. Design, 6, pp. 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, Calif.

2. LEGEND (Nishibata, Y. and A. Itai, Tetrahedron, 47, p. 8985 (1991)). LEGEND is available from Molecular Simulations, Burlington, Mass.

3. LeapFrog (available from Tripos Associates, St. Louis, Mo.).

Other molecular modeling techniques may also be employed in accordance with this invention. See, *e.g.*, Cohen, N. C. *et al.*, "Molecular Modeling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990). See also, Navia, M. A. and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Once a compound or binding agent has been designed or selected by the above methods, the efficiency with which that compound may bind to an IAP may be tested and optimized by computational evaluation.

A compound designed or selected as an IAP binding agent may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with the target site. Such non-complementary (*e.g.*, electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the binding agent and the IAP when the binding agent is bound to the IAP, preferably make a neutral or favorable contribution to the enthalpy of binding.

Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C (M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa., 1992); AMBER, version 4.0 (P. A. Kollman, University of California at San Francisco, 1994); QUANTA/CHARMM (Molecular Simulations, Inc., Burlington, Mass. 1994); and Insight II/Discover (Biosysm Technologies Inc., San Diego, Calif., 1994). These programs may be implemented, for example, using a Silicon Graphics workstation, IRIS 4D/35 or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known to those skilled in the art of which the speed and capacity are continually modified.

Once an IAP binding agent has been selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, *e.g.*, the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. Such substituted chemical compounds may then be analyzed for efficiency of fit to an IAP by the same computer methods described, above.

Conserved regions of the IAP family lend themselves to the methods and compositions of the invention. For example, recognition of mammalian IAP family members has provided emergent patterns of protein structure which can be used to design novel diagnostics and therapeutics as described herein. Recognition of patterns in this family allows for the design of modulators of apoptosis.

Functional fragments of IAP polypeptides such as, for example, fragments of survivin can be designed based on the crystal structure and atomic coordinates described herein. Fragments of a survivin polypeptide and the corresponding atomic coordinates of such fragments can be used in the modeling described herein. In addition, such fragments may be used to inhibit the apoptosis which occurs as part of disease or disorder processes. For example, a survivin fragment may be administered for the treatment of or prevention of apoptosis which occurs as a part of AIDS, neurodegenerative diseases, ischemic injury, toxin-induced liver disease and myelodysplastic syndromes.

In another embodiment of the present invention, the crystal structure and atomic coordinates are employed for the design of novel therapeutics. The apoptosis inhibiting capability of IAPs can be defined in an *in vitro* system known to detect alterations in apoptosis. Mammalian expression constructs carrying IAPs and their truncated forms can be introduced into various cell lines such as CHO, 3T3, HL60, Rat-1, or Jurkart cells, for example. In addition, SF21 insect cells may be used in which case the IAP gene is preferentially expressed using an insect heat shock promoter. Apoptosis will then be induced in transfected cells and controls employing standard methodologies (*e.g.*, serum withdrawal and staurosporine). A survival index (ratio of surviving transfected cells to surviving control cells) will indicate the strength of each IAP modulating or binding agent to inhibit or activate apoptosis. These experiments can confirm the presence of apoptosis inhibiting or enhancing activity and, can help to determine the minimal functional region of an IAP. Specific examples of apoptosis assays are provided in the following references: Lymphocyte: C. J. Li *et al.*, Science, 268:429-431, 1995; D. Gibellini *et al.*, Br. J. Haematol. 89:24-33, 1995; S. J. Martin *et al.*, J. Immunol. 152:330-42, 1994; C. Terai *et al.*, J. Clin Invest. 87:1710-5, 1991; J. Dhein *et al.*, Nature 373:438-441, 1995; P. D. Katsikis *et al.*, J. Exp. Med. 1815:2029-2036, 1995; Michael O. Westendorp *et al.*, Nature 375:497, 1995; DeRossi *et al.*, Virology 198:234-44, 1994. Fibroblasts: H. Vossbeck *et al.*, Int. J. Cancer 61:92-97, 1995; S. Goruppi *et al.*, Oncogene 9:1537-44, 1994; A. Fernandez *et al.*, Oncogene 9:2009-17, 1994; E. A. Harrington *et al.*, Embo J. 13:3286-3295, 1994; N. Itoh *et al.*, J. Biol. Chem. 268:10932-7, 1993. Neuronal Cells: G. Melino *et al.*, Mol. Cell. Biol. 14:6584-6596, 1994; D. M. Rosenbaum *et al.*, Ann. Neurol. 36:864-870, 1994; N. Sato *et al.*, J. Neurobiol 25:1227-1234, 1994; G. Ferrari *et al.*, J. Neurosci. 1516:2857-2866, 1995; A. K. Talley *et al.*, Mol. Cell Biol. 1585:2359-2366, 1995; A. K. Talley *et al.*, Mol. and Cell. Biol. 15:2359-2366, 1995; G. Walkinshaw *et al.*, J. Clin. Invest. 95:2458-2464, 1995. Insect Cells: R. J. Clem *et al.*, Science 254:1388-90, 1991; N. E. Crook *et al.*, J. Virol. 67:2168-74, 1993; S. Rabizadeh *et al.*, J. Neurochem. 61:2318-21, 1993; M. J. Birnbaum *et al.*, J. Virol 68:2521-8, 1994; R. J. Clem *et al.*, Mol. Cell. Biol. 14:5212-5222, 1994.

An IAP modulating agent or apoptosis modulating agent may be administered with a pharmaceutically-acceptable diluent, carrier, or excipient, in unit

dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer to a subject suffering from or presymptomatic for a IAP-associated carcinoma, for example. Any appropriate route of administration may be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, oral administration, or the like. Therapeutic formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets, capsules or the like; and for intranasal formulations, in the form of powders, nasal drops, aerosols, or the like.

Methods well known in the art for making formulations are found in, for example, Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co., 1405-1412, 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for IAP modulatory agents include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, liposomes, and the like. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

If desired, treatment with an IAP polypeptide, fragment thereof, or modulatory compound may be combined with other therapies for the disease such as, for example, surgery, radiation, or chemotherapy for cancers; surgery, steroid therapy, and chemotherapy for autoimmune diseases; antiviral therapies for AIDS; and for example, TPA for ischemic injury.

In addition, the binding agents identified by the methods of the invention can be used as a diagnostic in the detection or monitoring of conditions involving apoptosis associated disorders, IAP-associated disorders (*e.g.*, a survivin-associated disorder). Accordingly, a decrease or increase in the level of IAP production may provide an indication of a deleterious condition. Levels of IAP expression may be assayed by any standard technique. For example, binding agents of the invention can be used in immunoassays to detect or monitor IAP protein in a biological sample. IAP-specific polyclonal or monoclonal antibodies (produced by methods known in the art) may be used in any standard immunoassay format (*e.g.*, ELISA, Western blot, or RIA assay) to measure IAP polypeptide levels; comparisons are made to wild-type IAP levels, and a decrease in IAP production is indicative of a condition involving increased apoptosis.

The term "agent" as used herein describes any molecule, *e.g.* protein or pharmaceutical, with the capability of altering or mimicking the physiological function or expression of an IAP or survivin polypeptide. Generally, a plurality of agents are run in parallel at different concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, *i.e.* at zero concentration or below the level of detection.

Immunohistochemical techniques may also be utilized for IAP detection. For example, a tissue sample may be obtained from a patient, and a section stained for the presence of IAP using an anti-IAP antibody developed according to the methods of the invention and any standard detection system (*e.g.*, one which includes a secondary antibody conjugated to horseradish peroxidase). General guidance regarding such techniques can be found in, *e.g.*, Bancroft and Stevens (Theory and Practice of Histological Techniques, Churchill Livingstone, 1982) and Current Protocols in Molecular Biology, M. Ausubel *et al.*, eds., (Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., most recent Supplement).

The IAP diagnostic assays described above may be carried out using any biological sample (for example, any biopsy sample or bodily fluid or tissue) in which IAP is normally expressed.

In another embodiment, the invention provides a method for identifying an agent which interacts with or modulates expression or activity of an IAP or survivin polypeptide. Such method comprises contacting an agent and an IAP or survivin polypeptide, or a recombinant cell expressing an IAP or survivin polypeptide, under conditions sufficient to allow the agent to interact and determining the effect of the agent on the expression or activity of the polypeptide. The term "effect", as used herein, encompasses any means by which protein activity can be modulated, and includes measuring the interaction of the agent with the IAP or survivin molecule by physical means including, for example, fluorescence detection of the binding of an agent to the polypeptide. Such agents can include, for example, polypeptides, peptidomimetics, chemical compounds, small molecules and biologic agents. Examples of small molecules include but are not limited to small peptides or peptide-like molecules.

Contacting or incubating includes conditions which allow contact between the test agent and an IAP or survivin polypeptide, a cell expressing an IAP or survivin polypeptide or nucleic acid encoding a an IAP or survivin polypeptide. Contacting includes in solution and in solid phase. The test agent may optionally be a combinatorial library for screening a plurality of agents. Agents identified in the method of the invention can be further evaluated, detected, cloned, sequenced, and the like, either in solution or after binding to a solid support, by any method usually applied to the detection of a specific DNA sequence such as PCR, oligomer restriction (Saiki *et al.*, Bio/Technology, 3:1008-1012, 1985), oligonucleotide ligation assays (OLAs) (Landegren *et al.*, Science, 241:1077, 1988), and the like. Molecular techniques for DNA analysis have been reviewed (Landegren *et al.*, Science, 242:229-237, 1988).

Thus, the method of the invention includes combinatorial chemistry methods for identifying chemical agents that bind to or affect an IAP or survivin polypeptide expression or activity.

As yet another embodiment of the present invention, there are provided therapeutic methods which employ compounds and formulations as described herein. Agents that have been identified using invention methods can further be used to modulate an IAP or survivin polypeptide function in targeted organisms. Of particular

interest are agents that have a low toxicity or a reduced number of side effects for humans. ,

In addition, cells or organisms which have a mutations in an IAP or survivin polypeptide sequence may be used as models to screen for agents which modulate disorders associated with the mutation. A variety of mutations may be generated in critical domains of the survivin molecule, for example, the dimerization domains as described in Example 2. Such mutants create changes in the dimerization potential of survivin, which may also affect survivin function and binding properties. These mutants are also useful in generating alternative crystal structures to further analyze agents that could modulate IAP function or disorders.

The invention provides the first demonstration that the IAP survivin requires dimerization for activity. Accordingly, agents that inhibit dimerization can modulate the activity of survivin. Thus, it is desirable to identify such compounds to modulate the activity of survivin by binding, interacting, or effecting the dimerized form of survivin or can bind to, interact with, or otherwise effect a subunit (*e.g.*, a monomer) to prevent dimerization of the monomers thus preventing formation of survivin and thus modulating survivin activity. Mutants in the dimerization domain can also be used to identify such compounds.

The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLES

Example 1. Protein Purification

The cDNA of human survivin was amplified by PCR from a HeLa cell cDNA library. The wild-type and L54M point mutant (Quickchange, Stratagene) were expressed in *E. coli* using the pHIS8 expression vector encoding a thrombin cleavable N-terminal octahistidine tag (Jez *et al.*, Biochemistry 39 890-902, 2000). The L54M point mutant has substituted the amino acid at position 54 from leucine to methionine. The following mutants were similarly expressed, named X#Y, where

the amino acid at position # has been substituted from X to Y; mutants with substitutions at more than one amino acid position are designated as X#Y/X#Y: W10A, T34E, H80A, H80A/E76A, T97E, W10A/L98A/F101R/L102S, L6G/W10A/L98A/F101R/L102S, W10A/F93A/L98R, and L6G/W10A/F93A/L98R. The deletion mutant Δ126-142 was constructed by deleting amino acids 126-142 from the wild type survivin molecule.

Purification from *E. coli* lysates was accomplished using Ni^{2+} chelation chromatography by standard procedures (Jez, *supra.*). The histidine tag was removed by thrombin (Sigma) digestion during dialysis in 50 mM Tris (pH 8.0), 500 mM NaCl, and 20 mM β-mercaptoethanol at 4°C for 24 h. Samples were purified further over a Superdex 200 26/60 gel filtration column (Pharmacia) equilibrated in the dialysis/thrombin cleavage buffer. Peak fractions were collected and dialyzed against 5 mM HEPES-Na^+ (pH 7.5) and 1 mM DTT, concentrated to 15 mg/ml using Centricon10s (Amicon), and stored at -70°C.

Example 2. Oligomer Characterization

The dimeric association of survivin was established using static light scattering (miniDawn, Wyatt Technology, CA). Further quantification was accomplished using equilibrium sedimentation with the Beckman Optima XL-1 Analytical Ultracentifuge. Analysis was carried out at 20 °C using an An-60 Ti rotor. Survivin samples were diluted in 25 mM HEPES-Na^+ (pH 7.5), 100 and 500 mM NaCl, and 1 mM DTT. Samples of 0.10, 0.25, and 0.5 mg ml^{-1} were monitored by both absorbance at 280 nm and by interference with Rayleigh interference optics while being centrifuged at 10, 14, 20, and 28 × 10^3 rpm for 20 h to reach equilibrium. Data were analyzed using the Match7 and Reedit9 software (Jeff Lary, National Analytical Ultracentrifuge Facility).

Determination of the effective reduced molecular weight of survivin was carried out by the method of Johnson *et al.* (Biophys. J. 36:575-588, 1981) using the program WinnonIn. Data were fit to the exponential function $A = Ce^{\sigma}(r^2/2 - r^2_m/2)$,

where A is the absorbance at 280 nm, C is the fitting constant, r is the radial position, r_m is the radius of the meniscus, and σ is the effective reduced molecular weight.

Sedimentation velocity runs and hydrodynamic modeling were carried out using wild type survivin. Briefly, survivin was diluted to 1 mg ml^{-1} in 25 mM HEPES-Na+ (pH 7.5), 100 mM NaCl, 1 mM DTT. The sample was centrifuged at 45,000 rpm for 4 h at 20 °C. Sedimentation was monitored by fringe displacement and absorbance at 280 nm. Data sets were collected every 2 min. Determination of s^* from sedimentation velocity data was accomplished using the method of Philo (Biophys. J. 72:435-444, 1997) and Stafford (Anal. Biochem. 203:295-301, 1992) as incorporated in the programs SVEDBERG and DCDT. The partial specific volume of 0.73 cm^3 g^{-1} was calculated from the amino acid composition and used in hydrodynamic modeling with the program SEDNTERP.

To probe the relevance of each of the crystallographically observed dimers in solution, a C-terminal truncation was constructed, purified, and analyzed hydrodynamically. The deletion construct, Δ126-142, lacks all of the C-terminal hydrophobic patch on α6, which mediates the only other symmetric lattice contact observed in the survivin crystal. Hydrodynamic characterization of Δ126-142 survivin should unequivocally delineate which of the two crystallographically observed dimer interfaces is consistent with the dimer formed in solution. The survivin coil-less mutant spanning residues 1-99 would effectively disrupt both possible interfaces. Wild type, the L54M mutant, and Δ126-142 survivin are dimers in solution (Table 2).

Sedimentation equilibrium analysis of the Δ126-142 survivin truncation suggests that the second crystallographically observed dimerization interface mediated by residues 126-142 is unlikely to occur in solution. Additionally, sedimentation velocity experiments were used to measure wild type survivin's sedimentation coefficient (s^*) of 3.167 ± 0.001 S and its frictional ratio (f/f_0) of 1.201. Hydrodynamic modeling using these measurements and survivin's amino acid composition predict a prolate ellipsoid shape with a major axis of 111.2 Å and a minor axis of 27.6 Å. These values agree favorably with the measured tip-to-tip

interhelical distance of 111 Å and the measured distance across the center of the survivin dimer of 26 Å.

To probe the other crystallographically observed dimer interface, further point mutants of survivin were constructed and analyzed. These point mutants were characterized by gel filtration chromatography, equilibrium sedimentation analysis, and sedimentation velocity experiments. The average mass of these mutants as determined by sedimentation equilibrium is shown in Table 2. Survivin molecules with multiple mutations are listed with a "/" to indicate that more than one amino acid residue has been substituted.

TABLE 2. Average mass of survivin mutants determined by sedimentation equilibrium

Survivin mutants	Average Mass (kDa)
Wild-type survivin	35.65
W10A	34.02
T34E	30.55
L54M	34.84
H80A	34.50
H80A/E76A	34.76
T97E	33.50
W10A/L98A/F101R/L102S	27.84
L6G/W10A/L98A/F101R/L102S	24.72
W10A/F93A/L98R	31.67
L6G/W10A/F93A/L98R	30.38
Δ126-142	27.85

Example 3. Crystallography

Crystals of survivin were grown in hanging drops at 4°C by mixing 1.0 μl of survivin with 1.0 μl of a reservoir solution containing 100 mM HEPES-Na^+ (pH 7.5), 6-8% PEG 8000, 200 mM Li_2SO_4, and 2 mM dithiothreitol (DTT). Crystals were stabilized in 20% ethylene glycol, 100 mM HEPES-Na^+, 10% PEG 8000, 500 mM

Li_2SO_4, and 2 mM DTT and rapidly frozen in a 100 K stream of nitrogen gas. Multiple wavelength anomalous dispersion (MAD) data was collected around the Zn edge at the Stanford Synchrotron Radiation Laboratory, beamline 9-2 (Table 3).

Data were processed with DENZO and SCALEPACK (Otwinowski *et al.*, Meth. Enzymol. 276:307-326, 1997). The crystals contain two molecules per asymmetric unit (68% solvent) and belong to the space group C2 (a = 114.040 Å, b = 71.45 Å, c = 86.63, β = 133.370°). Three wavelength MAD data were scaled to the λ_3 data set using SCALEIT (Collaborative Computational Project, Acta Crystallogr. D. Biol. Crystallogr. 50:760-763 ,1994). Both zinc sites were located using SOLVE (Terwilliger *et al.*, Acta Crystallogr. D. Biol. Crystallogr. 55:849-861, 1999) and verified by inspection of both dispersive and anomalous difference Patterson maps using XTALVIEW (McRee, J. Mol. Graph. 10:44-46, 1992). MAD phasing was accomplished using SHARP (de La Fortelle *et al.*, Methods Enzymol. 276:472-494, 1997) and solvent flipping was carried out with SOLOMON (Abrahams *et al.*, Acta Crystallogr. D. Biol. Crystallogr. 52:30-42, 1996).

The initial model was built into experimental electron density maps displayed in O (Jones *et al.*, Acta Crystallogr. D. Biol. Crystallogr. 49:148-157, 1993). Two-fold averaging performed with DM (Cowtan *et al.*, Acta Crystallogr. D. Biol. Crystallogr. 54:487-493, 1998), using a mask generated from a partial model (residues 10 to 70) with the CCP4 program MAPMASK (Collaborative Computational Project, *supra.*), significantly improved the experimental maps. The model was rebuilt and then positionally refined against all the data using both figure of merit weighted phases from averaging and the observed structure factor amplitudes. A final round of refinement was accomplished using the observed amplitudes only. All refinements utilized the default bulk solvent model in CNS with maximum likelihood targets (Brunger *et al.*, Acta Crystallogr. D. Biol. Crystallogr. 54:905-921, 1998).

The current model includes 2 survivin molecules (residues 5 to 140 and 6 to 140), 2 zinc ions, 99 water molecules, and 3 sulphates. PROCHECK (Laskowski *et al.*, J. Appl. Crystallogr. 26:283-291, 1993) revealed a total of 80.8% of the residues are in the most favored region of the Ramachandran plot, with 18.4% in the additionally

allowed regions, and 0.8% in the generously allowed regions. Main chain and side chain structural parameters were consistently better than average (overall G value of 0.17). Surface area and dimer contacts were determined automatically with CNS and then verified manually in O.

Coordinates for the survivin dimer (accession code 1F3H) have been deposited in the Protein Data Bank.

TABLE 3. Data collection and refinement statistics

	λ_1	λ_2	λ_3
Wavelength (Å)	1.2830	1.2826	1.1271
Resolution Range (Å)	52.2 - 2.58	52.2 - 2.58	52.2 - 2.58
Observations	25,818	25,884	29,469
Unique reflections	13,582	13,611	15,366
Completeness[1] (%)	84.0 (37.6)	84.0 (37.5)	95.5 (92.0)
R_{sym}[1,2] (%)	3.4 (38.8)	3.3 (42.3)	3.6 (34.9)
POP_{iso}[3] (acentric/centric)	4.72/3.48	7.04/4.87	
POP_{ano}[3] (acentric)	2.45	2.65	
R_{cullis}[4] (iso/ano)	0.35/0.66	0.33/0.61	
R_{cryst}[5]/R_{free}[6] (%)			22.8/28.7
Protein atoms			2,215
Water molecules			89
Ligand atoms			15 sulfate, 2 zinc
R.m.s. deviations			
Bonds (Å)			0.025
Angles (°)			2.4
Average B-factor			
Protein (Å^2)			83.8
Water (Å^2)			65.4

[1] Number in parenthesis is for highest resolution shell.
[2] $R_{sym} = \Sigma | I_h - \langle I_h \rangle | / \Sigma I_h$, where $\langle I_h \rangle$ is the average intensity over symmetry equivalent reflections.
[3] Power of phasing = $\langle | F_{H(calc)} | / | E | \rangle$, where $F_{H(calc)}$ is the calculated difference and E is the lack of closure.
[4] $R_{cullis} = \Sigma | E | / \Sigma | F_{PH} - F_P |$.
[5] R-factor = $\Sigma | F_{obs} - F_{calc} | / \Sigma F_{obs}$, where summation is over the data used for refinement.
[6] R^{free} was calculated using 5% of data excluded from refinement.

Example 4. Caspase-3 Assay and Potential Binding Interactions

To test whether survivin physically interacts with caspase-3, *in vitro* binding assays were performed. The K_m (12μM) of caspase-3 for the tetrapeptide substrate, Z-DEVD-AFC, was determined by monitoring the initial enzymatic activity at room temperature in a reaction mixture containing 0.5 nM of recombinant caspase-3 (Calbiochem) and varying concentrations of Z-DEVD-AFC (Calbiochem) in 50 mM HEPES-Na^+ (pH 7.5), 150 mM KCl, 0.1% CHAPS, 5% glycerol and 5 mM DTT on a PTI Alphascan spectrofluorimeter (Photon Technology Instruments, Santa Clara, CA). Inhibition of caspase-3 by the aldehyde tetrapeptide DEVD-CHO (Calbiochem) was determined by monitoring enzymatic activity at room temperature in a reaction mixture containing 0.5 nM caspase-3, 200 μM Z-DEVD-AFC, and varying concentrations of this inhibitor. The apparent K_i value of 10 nM was determined by dividing the IC_{50} by (1 + [S]/Km) as previously shown, using the reported K_m of caspase-3 (Mittl *et al.*, J. Biol. Chem. 272:6539-6547, 1997).

Up to 30 μM of survivin exhibited no inhibitory effect on 50-500 pM caspase-3. An immunoprecipitation assay was used to establish that recombinant survivin and its mutants did not interact with caspase-3 *in vitro*. Stoichiometric amounts of survivin were mixed and incubated on ice followed by immunoprecipitation using anti-survivin anti-serum. The precipitated proteins and supernatants were subjected to immunoblotting using anti-caspase-3 anti-serum. No interactions between caspase-3 and the various survivin constructs were detected by immunoprecipitation. Moreover, no proteolytic cleavage of survivin occurred over the time course of the experiments or over a 48 h period during which 1.0 μM survivin was incubated with 1.0 nM caspase-3.

Example 5

Survivin expression is regulated in a cell cycle dependent manner with maximum levels occurring during the G2/M phase (Li *et al.*, 1998, *supra*). Immunofluorescence and imaging experiments demonstrate co-localization of

survivin with γ-tubulin at the spindle centrioles where survivin forms a shell with short radiating spokes around the γ-tubulin stained pericentriolar area. Additional studies revealed localization of both caspase-3 and the CDK inhibitor p21 $^{Waf1/Cip1}$ to this same structure. Furthermore, loss of caspase-3 from the spindle centrioles occurred following introduction of survivin antisense DNA into cells (Li, F., *et al.* Nature Cell Bio. 1:461-466, 1999). Survivin's high expression level in malignant tissue, including breast, lung, prostate, colon, pancreas, and stomach as well as neuroblastoma and lymphoma cells makes it an ideal target for cancer therapy (Tanaka, K. *et al.*, Clin. Cancer Res. 6:127-134, 2000; Monzo, M. *et al.*, J. Clinic Oncology 7:2100, 1999; Kawasaki, H. *et al.*, Cancer Res. 58:5071-5074, 1998; Lu *et al.* Cancer Res. 58:1808-1812, 1998; Jäätelä *et al.*, Exp. Cell Res. 248:30-43, 1999).

Bacterially expressed full length human survivin and the L54M mutant form a 35-kDa dimer in solution. The L54M point mutant was initially constructed to aid in MAD phasing using selenomethionine-substituted protein, however, selenomethionine substitution hindered crystal growth. Nevertheless, the unsubstituted L54M mutant crystallizes isomorphously with wild type survivin. Moreover, crystal quality was significantly higher yielding measurably better data. Characterization of the oligomeric form of survivin was accomplished using gel filtration chromatography, static light scattering, and equilibrium sedimentation by analytical ultracentrifugation.

Examination of survivin's crystalline lattice reveals two distinct dimerization interfaces. One fairly limited contact surface comprises the C-terminal half of $\alpha 6$ spanning residues 126-142. This region constitutes the C-terminal hydrophobic patch likely to mediate localization to the spindle centrosome. The other crystallographically observed dimerization interface, utilizing residues 6 to 10 in the N-terminal portion of the BIR domain and a 14 amino acid region encompassing residues 89 to 102 located just after the BIR domain, is significantly more extensive (Figs. 1a-f). The chemical features of this protein-protein interaction and the 1000 Å^2 of buried surface area of the dimerization interface bolsters the functional significance of this particular symmetric arrangement of monomers. The interfacial contacts are extensive considering the size of the survivin monomer, with residues 94

to 99 forming an intermolecular anti-parallel β-sheet at the dimer juncture (Figs. 1a-b and 1e). Hydrophobic contacts dominate the interaction surface with Leu 98 protruding from one monomer and extending into a hydrophobic pocket formed by Leu 6, Trp 10, Phe 93, Phe 101, and Leu 102 on the neighboring molecule (Fig. 1f). Sequence alignments of these residues with other BIR domain sequences show that the murine homologue of survivin should form an analogous dimer (Fig. 2).

Survivin's BIR domain is composed of a three-stranded anti-parallel β-sheet (residues 15 to 89) surrounded by four small α-helices (Figs. 1a-b). The tertiary fold of survivin's BIR domain closely resembles the reported NMR structure of the BIR2 domain of XIAP with a larger central β-sheet architecture (Sun *et al.*, Nature 401:818-822, 1999). A zinc ion tetrahedrally coordinated by Cys 57, Cys 60, His 77, and Cys 84 bridges the core β-sheet with α4 and α5 (Fig. 3a). One of survivin's most striking features is its 65 Å long C-terminal helix, α6, comprising residues 100 to 140 (Fig. 1a). Both hydrogen bonding and hydrophobic contacts between the BIR domain and residues in the first few turns of α6 stabilize and fix the direction of this helical rod. The remaining seven helical turns extend out and away from the BIR domain. The two α6 helices of the dimer form an approximate 110° angle while maintaining a tip-to-tip interhelical distance of 111 Å (Fig. 1b). This structural arrangement creates a curved and extended interface on one side of the survivin dimer.

Overall, survivin spatially organizes three separate and chemically distinct surfaces including acidic and basic patches on the BIR domain and a hydrophobic helical surface on α6. The BIR domain structure assembles a contiguous acidic surface made up primarily of residues in the core β-sheet. Residues from β2 (Asp 53), β3 (Glu 63, Glu 65), α4 (Glu 76), and the α3-α4 connecting loop (Glu 68, Asp 70, Asp 71, Asp 72) contribute to this highly charged and extensive surface (Figs. 1c-d). Residues 48 to 52 are unique to survivin and they form an acidic knuckle which protrudes from this patch. Given the number of potential survivin binding partners, this acidic region may represent one of the structural determinants that mediate electrostatic interactions between survivin's BIR domain and other proteins.

A second surface on the BIR domain together with the segment linking the BIR domain and α6 form an extensive basic patch (Figs. 1c-d). In addition, Lys 103,

Arg 106 and Lys 110, which form part of this basic cluster, sequester a sulfate ion derived from the crystallization solution on each survivin monomer in the asymmetric unit (Fig. 3b). While this crystallographic arrangement may simply reflect charge neutralization of this positive surface, sulphates sequestered in this manner often structurally correlate with regions likely to mediate phosphorylation dependent interactions. This sulfate-sequestering region precedes two putative phosphorylation sites as well as a C-terminal hydrophobic patch (Fig. 2). Phe 124, Ala 128, Val 131, Ala 134, Ile 135, and Leu 138 form a slightly twisted hydrophobic surface around the last half of α6 (Fig. 3c). Removal of this helical region results in a loss of survivin's localization to the spindle centrosomes with γ-tubulin and its ability to co-sediment with polymerized microtubules (Li *et al.*, Nature 396:580-583, 1998). The surface and residue composition of this helical hydrophobic cluster, its proximity to putative phosphate-binding and phosphorylation sites, along with the findings that the α6 helix mediates survivin localization, suggest a regulatory mechanism in which phosphorylation of survivin or its binding partners can abolish or potentiate a protein-protein interaction.

Zinc chelation appears essential for survivin function as mutation of Cys 84 to alanine abolishes survivin's ability to block apoptosis by acting as dominant negative mutant (Li, *supra.*). One explanation for this result may be due to the disruption of the BIR domain architecture necessary for a survivin-caspase-3 interaction. However, survivin's role, as a direct, physiologically relevant, caspase regulator remains controversial. Mutational analysis of XIAP reveals that the most important residues for caspase-3 inhibition reside in a loop N-terminal to XIAP's BIR2 domain (Sun, *supra.*) (Fig. 2). Survivin lacks this N-terminal extension, and would be predicted to act as an inefficient caspase inhibitor. Furthermore, inhibition of expression of the *C. elegans* survivin homologue *bir-1* in embryos results in a cytokinesis defect rather than an apoptotic event (Fraser *et al.*, Current Biol. 9:292-301 (1999)). This is not entirely unexpected, as BIR domain containing proteins have been found in organisms with no known caspases, including *S. cerevisiae* and *S. pombe* (Uren *et al.*, Proc. Natl. Acad. Sci. 96:10170-10175, 1999). Disruption of these genes results in a variety of meiotic and mitotic defects, including failure to elongate the mitotic spindle in fission yeast (Xu *et al.*, Mol. Cell 3:389-395, 1999).

In order to investigate the caspase inhibitory functions of properly folded, full length survivin, both recombinant wild type survivin and the L54M point mutant were each tested for their ability to block caspase-3 activity. Neither of the samples tested affected caspase-3 proteolytic cleavage of the fluorogenic peptide Z-DEVD-AFC. In contrast, the reversible caspase inhibitor DEVD-CHO displayed potent caspase-3 inhibition (K_I =10 nM). Additionally, assays performed with the BIR2-containing full-length cIAP1/hMIHB or with cIAP1/hMIHB lacking its BIR1 domain resulted in significant levels of caspase-3 inhibition (K_I =40 nM) similar to those previously reported (Roy *et al.*, EMBO J. 16:6914-6925, 1997). The current work suggests that human survivin is not a direct caspase inhibitor and supports the recent proposal that survivin's anti-apoptotic function results from an indirect inhibitory role of caspase-3 by promoting a pro-caspase-3/p21 complex (Suzuki *et al.*, Oncogene 19:1346-1353 2000). This does not exclude the possibility that survivin and caspase-3 interact nor that survivin promotes inhibition of caspase activity during mitosis (Tamm *et al.*, Cancer Res. 58:5315-5320, 1998).

In summary, recombinantly expressed, full length human survivin forms a symmetric dimer with two BIR domains and two extended helices. Survivin's BIR domain lacks the region previously mapped as necessary for caspase inhibition and is incapable of blocking proteolytic cleavage of the preferred caspase-3 peptide substrate DEVD. The orientation and length of the dimer's two C-terminal helices suggest that survivin could bridge multiple γ-tubulin molecules. Survivin may act as a structural adapter spanning γ-tubulin monomers or a gamma-tubulin complex protein (GCP) during formation of the microtubule nucleation complex. This structural role mediated by α6, would localize survivin's BIR domains to the same site possibly resulting in the recruitment of other proteins to the MTOC, including p21, caspase-3, and CDK4 (Suzuki, *supra.*). Survivin's ability to block apoptosis may be due to increased local concentrations of cell death proteins and anti-apoptotic factors near the MTOC, thereby, elevating caspase inhibition and protecting the MTOC from proteolysis. The functional consequences of these events are directly dependent on survivin's three-dimensional structure. Solvent-exposed hydrophobic patches and to a lesser extent constellations of identically charged amino acid side chains are generally energetically disfavored when not engaged with binding

partners. These regions, all of which are found in survivin, are often maintained for functionally important interactions. As such, the work described herein provides specific structural targets for functional experiments.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

What is claimed is:

1. A method of predicting a binding agent for an inhibitor of apoptosis protein (IAP), said method comprising:

(a) modeling a potential binding agent that interacts with one or more domains of a survivin polypeptide or fragment thereof, defined by a plurality of atomic coordinates of the survivin polypeptide or fragment thereof; and

(b) determining the ability of said potential binding agent to modulate a survivin biological function, thereby predicting an IAP binding agent.

2. The method of claim 1, wherein the survivin polypeptide or fragment thereof is a vertebrate survivin polypeptide.

3. The method of claim 2, wherein the survivin polypeptide or fragment thereof is a mammalian polypeptide.

4. The method of claim 3, wherein the survivin polypeptide or fragment thereof is a mouse or human polypeptide.

5. The method of claim 1, wherein the survivin polypeptide or fragment thereof has a sequence selected from the group consisting of:

(a) SEQ ID NO: 3;
(b) conservative substitutions of (a);
(c) variants of (a);
(d) mutants of (a), (b), or (c); and
(e) fragments of (a), (b), (c), or (d).

6. The method of claim 5, wherein the mutant survivin is more hydrophilic than wild-type survivin.

7. The method of claim 6, wherein the mutant survivin has a sequence selected from the group consisting of:

(a) SEQ ID NO: 4;

(b) conservative substitutions of (a);

(c) variants of (a); and

(d) fragments of (a), (b), or (c).

8. The method of claim 5, wherein the mutant survivin is selected from the group consisting of W10A, T34E, L54M, H80A, H80A/E76A, T97E, W10A/L98A/F101R/L102S, L6G/W10A/L98A/F101R/L102S, W10A/F93A/L98R, L6G/W10A/F93A/L98R and Δ126-142.

9. The method of claim 8, wherein a conservative substitution, variant or fragment of the selected mutant survivin is used.

10. The method of claim 1, wherein the plurality of atomic coordinates are as set forth in Table 1.

11. The method of claim 1, wherein the potential binding agent is selected from the group consisting of a peptide, an antibody, a peptidomimetic, and a small molecule.

12. The method of claim 1, wherein the biological activity of survivin is inhibited by said binding agent.

13. The method of claim 1, wherein the biological activity of survivin is increased by said binding agent.

14. The method of claim 1, wherein the domain is a baculovirus IAP repeat (BIR) domain of survivin.

15. The method of claim 12, wherein the binding agent binds to the N-terminal portion of the BIR domain.

16. The method of claim 1, wherein the domain is a C-terminal helix of survivin.

17. The method of claim 16, wherein the C-terminal helix comprises residues 100 to 140 of SEQ ID NOs: 3 or 4, conservative substitutions thereof, variants thereof, or mutants thereof.

18. The method of claim 1, wherein the binding agent is modeled to bind to amino acid residues 89-102 of SEQ ID NOs: 3 or 4, conservative substitutions thereof, variants thereof, or mutants thereof.

19. The method of claim 1, wherein the binding agent is modeled to bind to amino acid 48-52 of SEQ ID NOs: 3 or 4, conservative substitutions thereof, variants thereof, or mutants thereof.

20. The method of claim 1, wherein said potential binding agent is designed de novo.

21. The method of claim 1, wherein the binding agent is designed from a known binding agent.

22. The method of claim 1, wherein the binding agent is identified using a computer algorithm to predict a three-dimensional representation of the potential binding agent based upon a three-dimensional representation of the survivin polypeptide or fragment thereof.

23. The method of claim 1, wherein the biological function is dimerization activity; tubulin interaction activity; p21, caspase-3 and CDK4 requirement activity; or zinc chelation activity.

24. A method of identifying an inhibitor of apoptosis protein (IAP) binding agent, said method comprising:

(a) defining a survivin polypeptide or fragment thereof based on a plurality of atomic coordinates of the survivin polypeptide;

(b) modeling a potential binding agent that interacts with a domain of the survivin polypeptide;

(c) contacting the potential binding agent with the survivin polypeptide; and

(d) determining the ability of said potential binding agent to modulate a survivin biological function, thereby identifying a survivin binding agent.

25. An IAP binding agent identified by the method of claim 1.

26. A method for increasing apoptosis in a cell with a cell proliferative disorder, said method comprising contacting the cell with the binding agent of claim 22 in an amount effective to inhibit IAP activity.

27. The method of claim 26, wherein the binding agent is an antibody.

28. The method of claim 26, wherein the binding agent is selected from the group consisting of a peptide, a peptidomimetic, and a small molecule.

29. The method of claim 26, wherein the cell proliferative disorder is cancer.

30. The method of claim 26, wherein the cell is derived from a tissue selected from the group consisting of ovary, breast, pancreas, lymph node, skin, blood, lung, brain, kidney, liver, nasopharyngeal cavity, thyroid, central nervous system, prostate, colon, rectum, cervix, and endometrium.

31. The method of claim 26, wherein the IAP activity is survivin activity.

32. A method for treating a mammal diagnosed as having a cell proliferative disorder, said method comprising contacting the mammal with the binding agent of claim 22 in an amount effective to inhibit IAP activity.

33. The method of claim 32, wherein the binding agent is an antibody.

34. The method of claim 32, wherein the binding agent is selected from the group consisting of a peptide, a peptidomimetic, and a small molecule.

35. The method of claim 32, wherein the cell proliferative disorder is cancer.

36. The method of claim 32, wherein the cell is derived from a tissue selected from the group consisting of ovary, breast, pancreas, lymph node, skin, blood, lung, brain, kidney, liver, nasopharyngeal cavity, thyroid, central nervous system, prostate, colon, rectum, cervix, and endometrium.

37. A method of detecting survivin in a sample, said method comprising contacting the sample with the binding agent of claim 25 and detecting the binding of the agent to survivin.

38. A method for identifying an agent that enhances apoptosis, said method comprising:

(a) modeling a potential apoptosis enhancing agent that interacts with one or more domains of a survivin polypeptide or fragment thereof, defined by a plurality of atomic coordinates of the survivin polypeptide; and

(b) determining the ability of said potential apoptosis enhancing agent to modulate apoptosis, thereby identifying an apoptosis enhancing agent.

39. A computer program on a computer readable medium, said computer program comprising instructions to cause a computer to:

(a) define a survivin polypeptide or fragment thereof based on a plurality of atomic coordinates of the survivin polypeptide; and

(b) model a potential survivin activity modulating agent that interacts with the survivin polypeptide.

40. The computer program of claim 39, wherein the plurality of atomic coordinates are as set forth in Table 1.

41. An isolated crystalline survivin polypeptide.

42. The crystalline survivin polypeptide of claim 41, wherein the survivin polypeptide has a sequence selected from the group consisting of:

(a) SEQ ID NO: 3;

(b) conservative substitutions of (a);

(c) variants of (a);

(d) mutants of (a), (b), or (c); and

(e) fragments of (a), (b), (c), or (d).

43. The method of claim 42, wherein the mutant survivin is more hydrophilic than wild type survivin.

44. The method of claim 43, wherein the mutant survivin has a sequence selected from the group consisting of:

(a) SEQ ID NO: 4;

(b) conservative substitutions of (a);

(c) variants of (a); and

(d) fragments of (a), (b), or (c).

45. The method of claim 42, wherein the mutant survivin is selected from the group consisting of W10A, T34E, L54M, H80A, H80A/E76A, T97E, W10A/L98A/F101R/L102S, L6G/W10A/L98A/F101R/L102S, W10A/F93A/L98R, L6G/W10A/F93A/L98R and Δ126-142.

46. The method of claim 45, wherein a conservative substitution, variant or fragment of the selected mutant survivin is used.

47. The crystalline survivin polypeptide of claim 41, wherein the atomic coordinates of the atoms of the survivin polypeptide are as set forth in Table 1.

48. A method for identifying an agent which inhibits dimerization of a survivin polypeptide, the method comprising:

(a) contacting the agent and a survivin polypeptide under conditions sufficient to allow the agent and survivin to interact; and

(b) determining the effect of the agent on the ability of survivin polypeptide to demerit.

49. The method of claim 48, wherein the agent is a peptide.

50. The method of claim 48, wherein the agent is a peptidomimetic.

51. The method of claim 48, wherein the survivin polypeptide is expressed in a cell.

52. The method of claim 48, wherein the ability of the agent to modulate dimerization is determined by detection of a change in apoptosis.

53. The method of claim 48, wherein the survivin polypeptide has a sequence selected from the group consisting of:

(a) SEQ ID NO: 3;

(b) conservative substitutions of (a);

(c) variants of (a);

(d) mutants of (a), (b), or (c); and

(e) fragments of (a), (b), (c), or (d).

54. The method of claim 53, wherein the mutant survivin is selected from the group consisting of W10A, T34E, L54M, H80A, H80A/E76A, T97E, W10A/L98A/F101R/L102S, L6G/W10A/L98A/F101R/L102S, W10A/F93A/L98R, L6G/W10A/F93A/L98R and Δ126-142.

55. The method of claim 54, wherein a conservative substitution, variant or fragment of the selected mutant survivin is used.

56. A method for identifying an agent that enhances apoptosis, said method comprising:

(a) defining a survivin polypeptide or fragment thereof based on a plurality of atomic coordinates of the survivin polypeptide;

(b) modeling a potential apoptosis enhancing agent that interacts with the survivin polypeptide;

(c) contacting the potential apoptosis enhancing agent with the survivin polypeptide; and

(d) determining the ability of the agent to enhance apoptosis of a cell, thereby identifying the apoptosis enhancing agent.

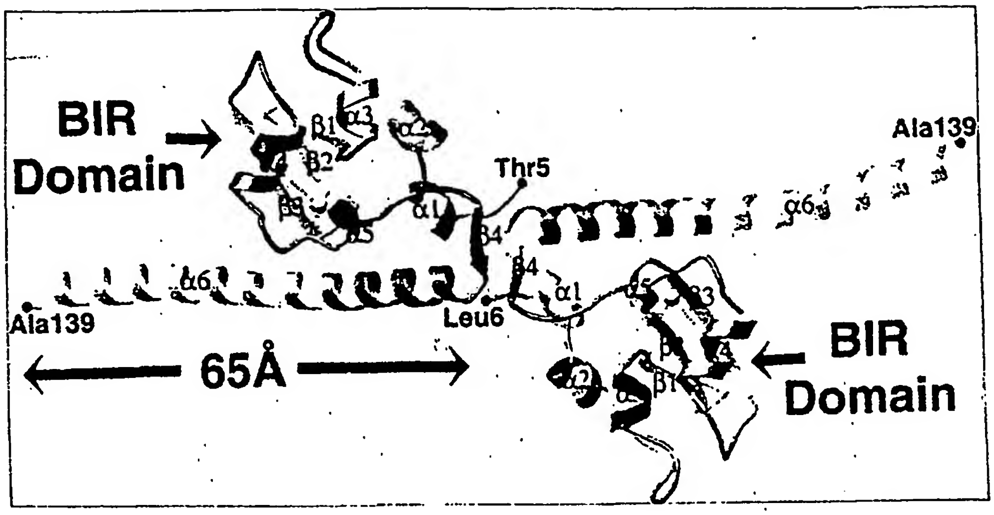

BIR Domain
Ala139
Thr5
α6
Leu6
65Å
BIR Domain

FIG. 1a

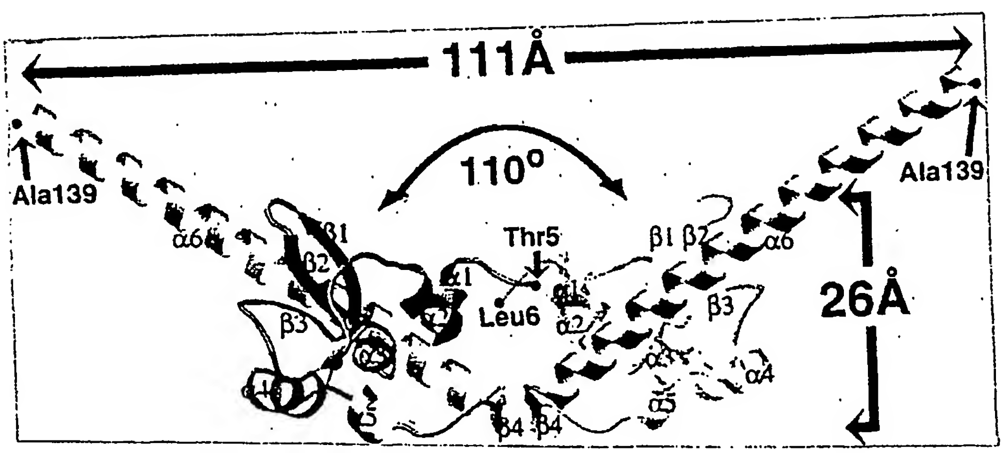

111Å
110°
Ala139
Thr5
Leu6
26Å
Ala139

FIG. 1b

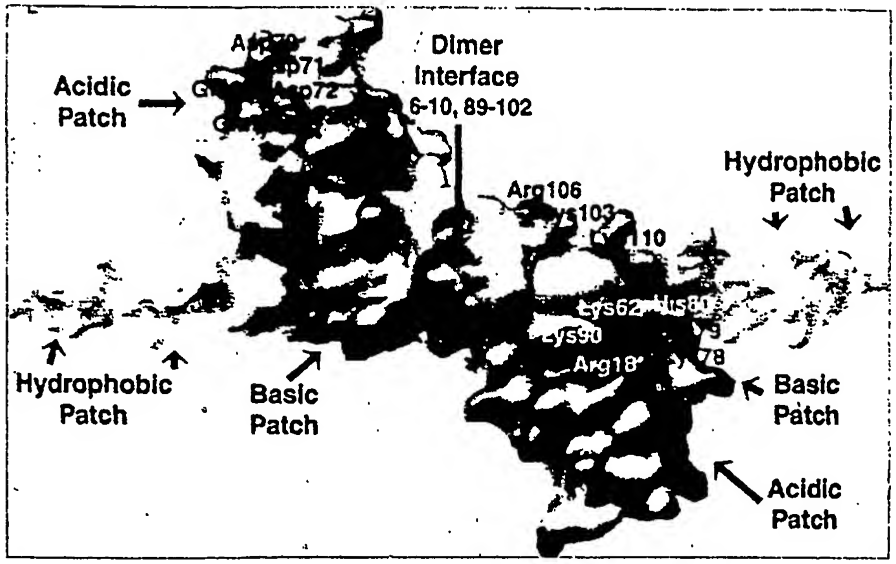

Acidic Patch
Dimer Interface 6-10, 89-102
Hydrophobic Patch
Arg106
Lys62
Lys90
Hydrophobic Patch
Basic Patch
Basic Patch
Acidic Patch

FIG. 1c

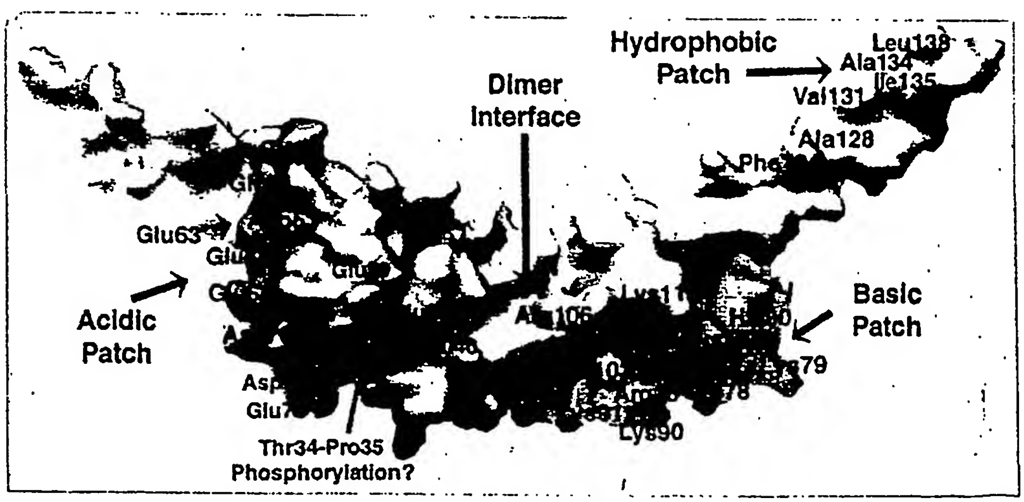

Hydrophobic Patch
Leu138
Ala134
Val131
Ala128
Dimer Interface
Glu63
Acidic Patch
Basic Patch
Lys90
Thr34-Pro35 Phosphorylation?

FIG. 1d

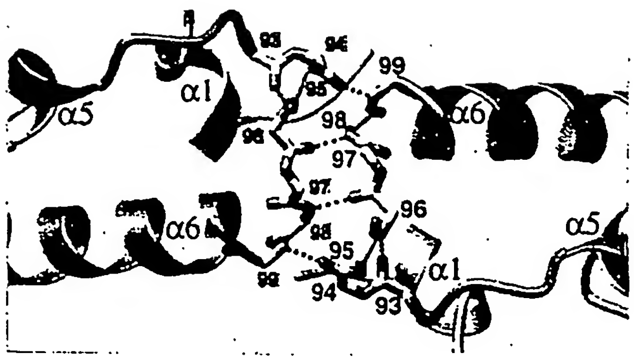

α5
α1
99
98
97
96
95
94
93
α6
α5
α1

FIG. 1e

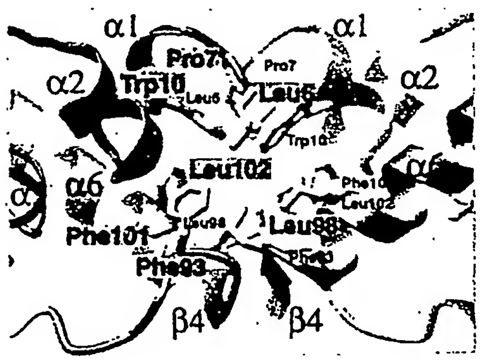

α1
α1
Pro7
Pro7
α2
Trp10
Leu6
α2
Leu102
α6
Phe101
Leu98
Phe93
β4
β4

FIG. 1f

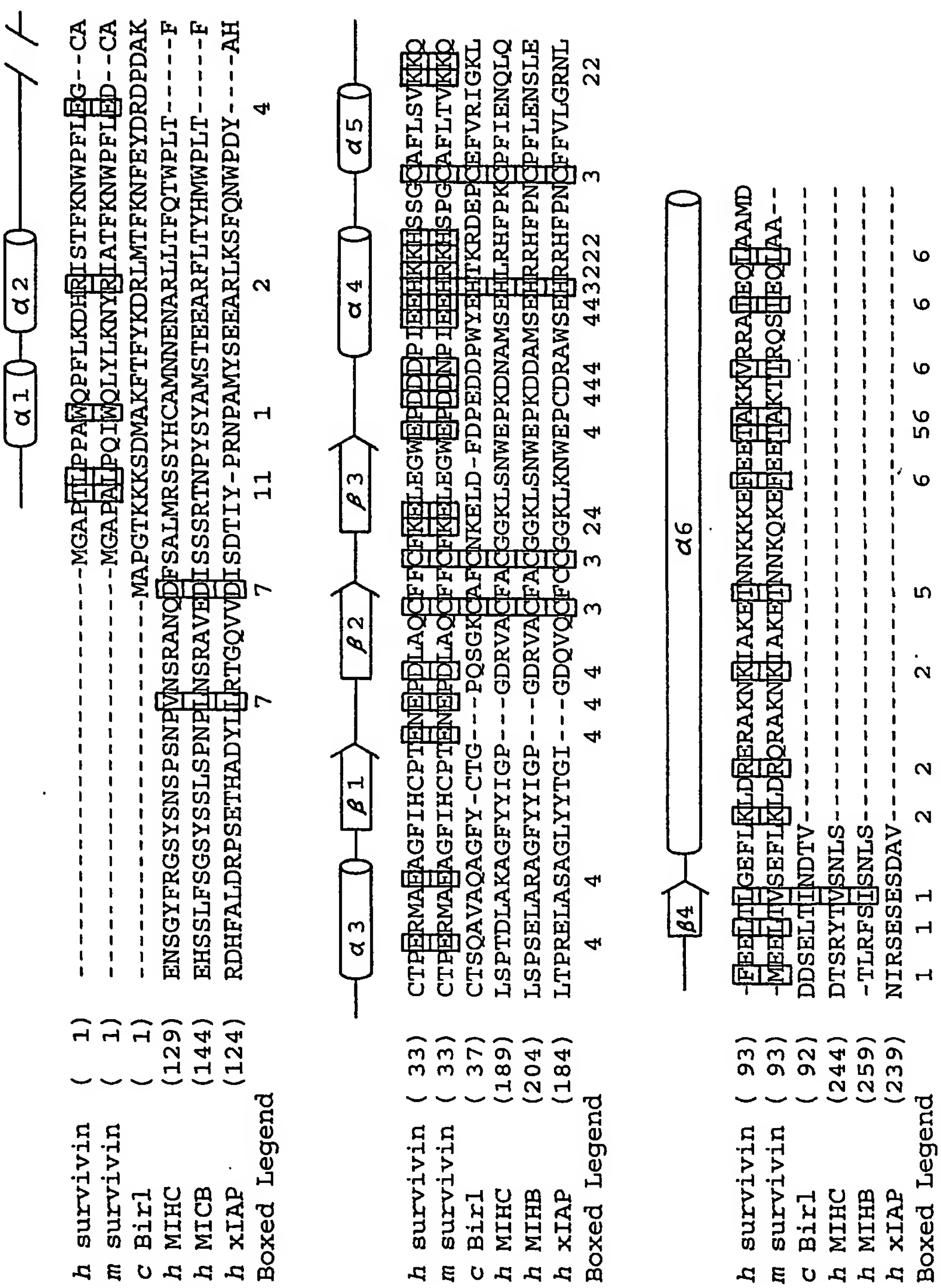

α1 α2
h survivin (1) ---------------MGAPTLPPAWQPFLKDHRISTFKNWPFLEG--CA
m survivin (1) ----------------MGAPALPQIWQLYLKNYRIATFKNWPFLED--CA
c Birl (1) -----------------MAPGTKKSDMAKFTFYKDRLMTFKNFEYDRDPDAK
h MIHC (129) ENSGYFRGSYSNSPSNPVNSRANQDFSALMRSSYHCAMNNENARLLTFQTWPLT-----F
h MICB (144) EHSSLFSGSYSSLSPNPLNSRAVEDISSSRTNPYSYAMSTEEARFLTYHMWPLT-----F
h xIAP (124) RDHFALDRPSETHADYLLRTGQVVDISDTTY-PRNPAMYSEEARLKSFQNWPDY----AH
Boxed Legend 7 7 7 11 1 2 4
α3 β1 β2 β3 α4 α5
h survivin (33) CTPERMAEAGFIHCPTENEPDLAQCFFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQ
m survivin (33) CTPERMAEAGFIHCPTENEPDLAQCFFCFKELEGWEPDDNPIEEHRKHSPGCAFLTVKKQ
c Birl (37) CTSQAVAQAGFY-CTG---PQSGKCAFCNKELD-FDPEDDPWYEHTKRDEPCEFVRIGKL
h MIHC (189) LSPTDLAKAGFYYIGP---GDRVACFACGGKLSNWEPKDNAMSEHLRHFPKCPFIENQLQ
h MIHB (204) LSPSELARAGFYYIGP---GDRVACFACGGKLSNWEPKDDAMSEHRRHFPNCPFLENSLE
h xIAP (184) LTPRELASAGLYYTGI---GDQVQCFCCGGKLKNWEPCDRAWSEHRRHFPNCFFVLGRNL
Boxed Legend 4 4 4 4 4 3 3 3 24 4 444 443222 3 22
β4 α6
h survivin (93) -EELTLGEFLKLDRERAKNKIAKETNNKKKEFEETAKKVRRAIEQLAAMD
m survivin (93) -MEELTVSEFLKLDRQRAKNKIAKETNNKQKEFEETAKTTRQSIEQLAA--
c Birl (92) DDSELTINDTV--
h MIHC (244) DTSRYTVSNLS--
h MIHB (259) -TLRFSISNLS--
h xIAP (239) NIRSESESDAV--
Boxed Legend 1 1 1 2 2 2 5 5 6 56 6 6 6 6

FIG. 2

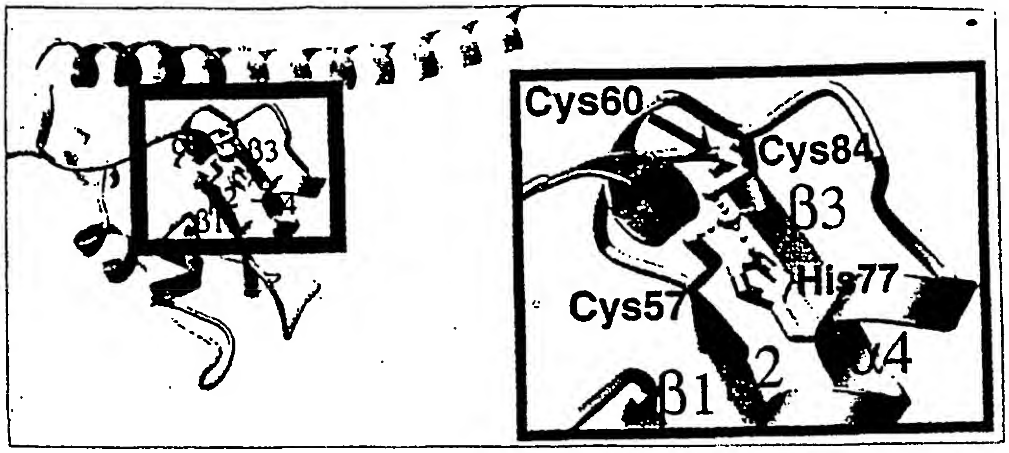


FIG. 3a

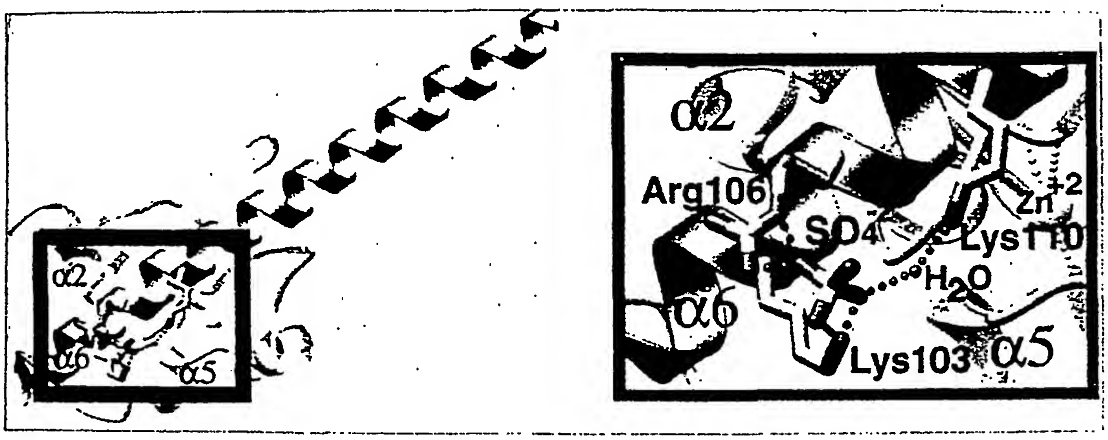


FIG. 3b

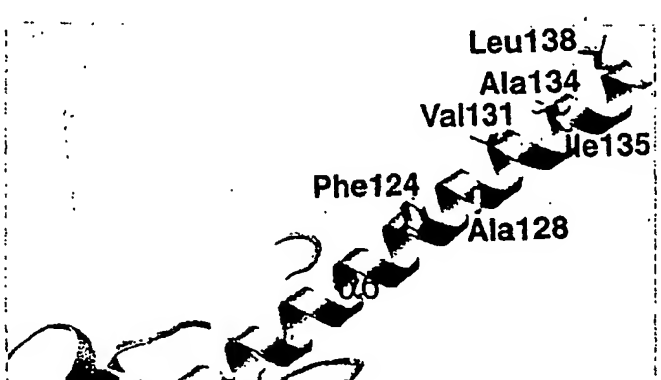


FIG. 3c

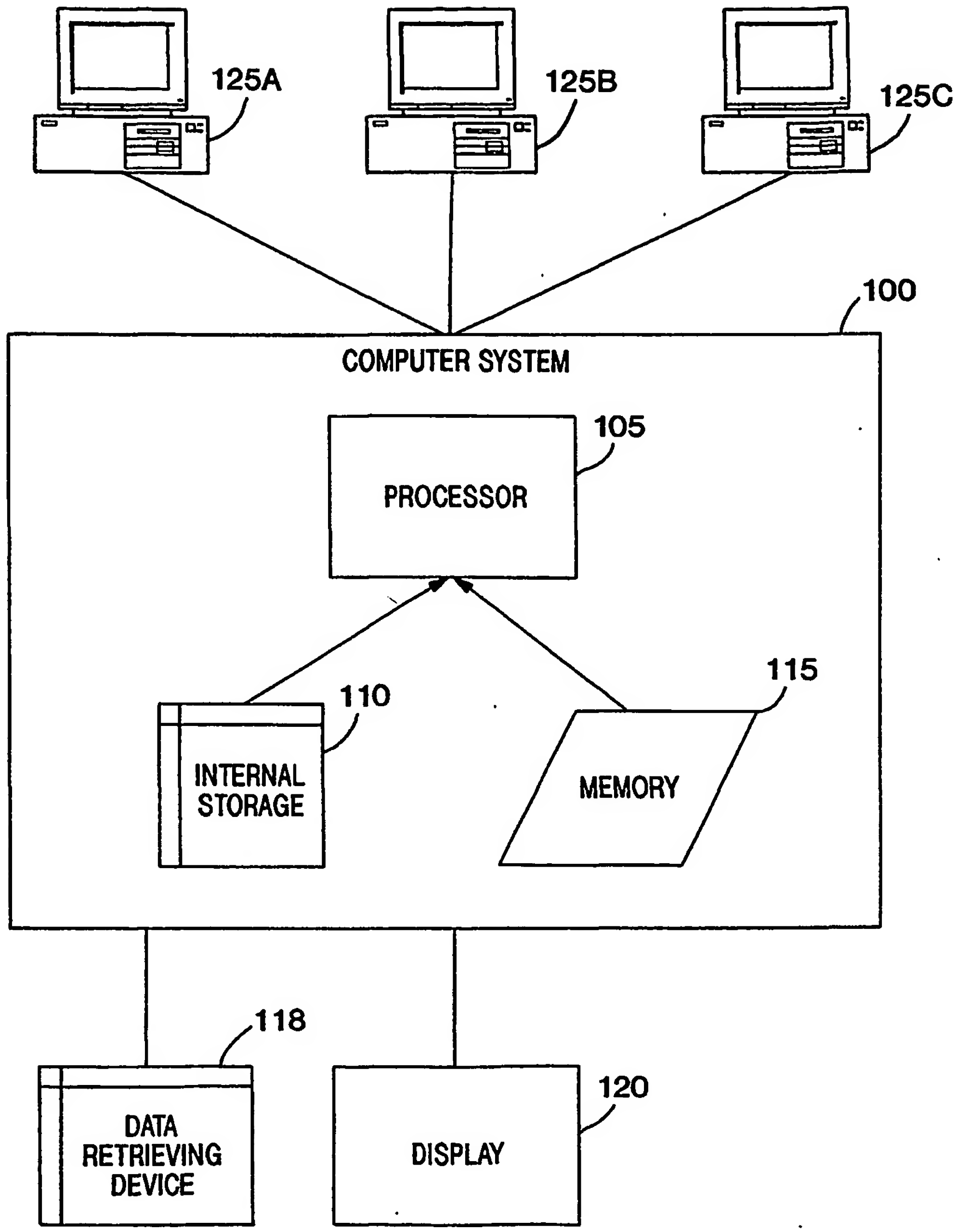

125A
125B
125C
100
COMPUTER SYSTEM
105
PROCESSOR
110
INTERNAL STORAGE
115
MEMORY
118
DATA RETRIEVING DEVICE
120
DISPLAY

FIG. 4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/002622 A3

(51) International Patent Classification[7]: G01N 33/68, C07K 16/18, A61K 39/395, C30B 29/58, C07K 14/47

(21) International Application Number: PCT/US01/20872

(22) International Filing Date: 29 June 2001 (29.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/608,352 29 June 2000 (29.06.2000) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/608,352 (CIP)
Filed on 29 June 2000 (29.06.2000)

(71) Applicant (*for all designated States except US*): THE SALK INSTITUTE FOR BIOLOGICAL STUDIES [US/US]; 10010 North Torrey Pines Road, San Diego, CA 92037 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): NOEL, Joseph, P. [US/US]; 7280 Park Village Road, San Diego, CA 92129 (US). VERDACIA, Mark [US/US]; 415 Gravilla Street, #11, La Jolla, CA 92037 (US). HUNTER, Tony [GB/US]; 4578 Vista De La Patria, Del Mar, CA 92015 (US). HUANG, Han-Kuei [—/US]; 5438 Lauretta Street, Apt. A, San Diego, CA 92110 (US).

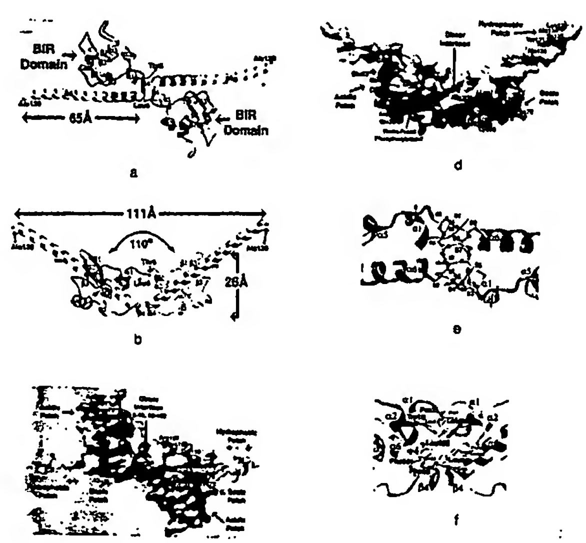
(74) Agents: REITER, Stephen, E. et al.; Foley & Lardner, P.O. Box 80278, San Diego, CA 92138-0278 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: CRYSTAL STRUCTURE OF SURVIVIN



a d b e c f

(57) Abstract: Provided is the structure of an inhibitor of apoptosis protein (IAP). Å 2.58 A crystal structure of a human survivin point mutant (L54M) determined by Multiple Wavelength Anomalous Dispersion (MAD) using the endogenously bound Zn^{+2} ions is provided. Methods of using the crystal structure and atomic coordinates fo the development of IAP binding agents is also provided. In addition, the disclosure provides computer programs on computer readable medium for use in developing iAP binding agents.

WO 02/002622 A3

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 12 September 2002

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 01/20872

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/68 C07K16/18 A61K39/395 C30B29/58 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K G01N C30B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 22589 A (UNIV YALE ;ALTIERI DARIO C (US)) 28 May 1998 (1998-05-28)	1-5, 10-22, 24-42, 47,56
Y	the whole document	1-24, 38-40, 43-46,56
	especially page 19, lines 19-2	

Y	HINDS MARK G ET AL: "Solution structure of a baculoviral inhibitor of apoptosis (IAP) repeat." NATURE STRUCTURAL BIOLOGY, vol. 6, no. 7, July 1999 (1999-07), pages 648-651, XP008004532 ISSN: 1072-8368 the whole document	1-24, 38-40,56

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2002	02/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van der Schaal, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 2000 (2000-05) ITO TAKESHI ET AL: "Survivin promotes cell proliferation in human hepatocellular carcinoma." Database accession no. PREV200000239207 XP002201893 abstract & HEPATOLOGY, vol. 31, no. 5, May 2000 (2000-05), pages 1080-1085, ISSN: 0270-9139 ---	23
Y	DOUBLIE S: "PREPARATION OF SELENOMETHIONYL PROTEINS FOR PHASE DETERMINATION" METHODS IN ENZYMOLOGY, ACADEMIC PRESS INC, SAN DIEGO, CA, US, no. 276, 1997, pages 523-530, XP001053309 ISSN: 0076-6879 the whole document especially page 529 'Introduction of Methionines' ---	6-9, 43-46, 53-55
A	KUNTZ I D ET AL: "STRUCTURE-BASED MOLECULAR DESIGN" ACCOUNTS OF CHEMICAL RESEARCH, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 27, no. 5, May 1994 (1994-05), pages 117-123, XP000885741 ISSN: 0001-4842 the whole document ---	1-24, 38-40,56
A	DEVERAUX QUINN L ET AL: "IAP family proteins: Suppressors of apoptosis" GENES AND DEVELOPMENT, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, US, vol. 13, no. 3, 1 February 1999 (1999-02-01), pages 239-252, XP002175394 ISSN: 0890-9369 ---	
P,X	VERDECIA MARK A ET AL: "Structure of the human anti-apoptotic protein survivin reveals a dimeric arrangement." NATURE STRUCTURAL BIOLOGY, vol. 7, no. 7, July 2000 (2000-07), pages 602-608, XP002201890 ISSN: 1072-8368 the whole document --- -/--	1-56

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 01/20872

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MUCHMORE STEVEN W ET AL: "Crystal structure and mutagenic analysis of the inhibitor-of-apoptosis protein survivin." MOLECULAR CELL, vol. 6, no. 1, July 2000 (2000-07), pages 173-182, XP002201891 ISSN: 1097-2765 the whole document	1-56
P,X	CHANTALAT LAURENT ET AL: "Crystal structure of human survivin reveals a bow tie-shaped dimer with two unusual alpha-helical extensions." MOLECULAR CELL, vol. 6, no. 1, July 2000 (2000-07), pages 183-189, XP002201892 ISSN: 1097-2765	1-5, 10-42, 47-52,56
Y	the whole document	6-9, 43-46, 53-55

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

International application No.
PCT/US 01/20872

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 26-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 25, 26, 28-32, 34-37 relate to (the use of) a product defined by reference to a desirable characteristic or property, namely being able to interact with one or more domains of a survivin polypeptide or fragment thereof.

The claims cover (the use of) all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to antibodies against survivin

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/20872

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9822589	A	28-05-1998	US	6245523	B1	12-06-2001
			AU	736587	B2	02-08-2001
			AU	7301898	A	10-06-1998
			EP	0950103	A2	20-10-1999
			JP	2002514060	T	14-05-2002
			WO	9822589	A2	28-05-1998